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SAKEL'S PHARMACOLOGIC SHOCK TREATMENT FOR SCHIZOPHRENIA

TENTATIVE DIRECTIONS AND SYSTEM OF RECORDING *

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The following directions apply to Sakel's insulin shock treatment [1] for schizophrenia as it was reported and developed at the university clinic at Vienna in 1933. This procedure occupies a unique position, and both the therapeutic results and the precautionary measures are dependent on purely empirical rules. These rules are particularly important because there has so far been no satisfactory explanation of the mechanisms involved in the insulin shock treatment.

The purpose of these directions is to establish a single standard method and a single standard descriptive terminology, so that the results of the treatment can be compared and determined. This should eliminate misunderstandings due either to variation in the procedure or to uncertainties involved in statistical tabulations.

The procedure is based on a consideration of the literature and on the clinical experiences gathered at the university clinic in Vienna (director: Prof. Otto Pötzl), the psychiatric institute Zofjówka Otwock, Warsaw (director: Dr. J. P. Frostig) and the cantonal psychiatric institute at Münsingen, Switzerland (director: Dr. Max Müller).

It will be assumed that the reader is already acquainted with the literature on the insulin therapy for schizophrenia.

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1. These directions were discussed at two successive meetings of the pathologic seminar, at the university psychiatric and neurologic clinic, Vienna. Those who participated in the discussion were: Professor Pötzl, docent Hoff, Dr. Dussik, Dr. Palisa, Dr. Silberpfennig, Dr. Pappenheim and Dr. Pisk. Final comments on the completed report were made by Dr. Sakel and Docent Müller.

Prof. Pötzl, Dr. Sakel, Docent Müller and Dr. Dussik made suggestions, comments and corrections.

MATERIAL

Since the concept of schizophrenia is variously defined and may therefore lead to misunderstandings, it is desirable to designate what one understands by the term. My associates and I treat conditions which are sometimes described as paraphrenia (Bumke) and are now usually distinguished from genuine schizophrenia. We also believe that treatment is worth while in cases of incipient paranoid development (Kehrer; Lange). For the present, the form described by Ewald and Specht is for theoretical reasons excluded from treatment. We believe also that it is better to exclude from statistical tabulations cases of amentia (i. e., acute confusional psychosis) in which there is no indication of a schizophrenic process in the history. We treat the following forms according to the classification of Claude: paranoia, the schizoses and dementia praecox. Other French classifications describe the following borderline forms which come under statistical consideration: *délire d'interprétation, psychose hallucinatoire chronique* (Sérieux and Capgras) and *délires progressifs* (Dide and Guiraud).

It is desirable to give separate statistical consideration to forms (fantastic and eccentric types) which are allied to simple schizophrenia and in which differential diagnostic difficulties due to paranoid and schizoid developments are likely to occur.

In the final evaluation of the specific effect of insulin on the schizophrenic process it will be of importance to analyze its action on the various special types.

A distinction must be made between schizophrenia with a continuously progressive course and the type with an intermittent course. In an evaluation of the therapeutic result the first group is the more important. With intermittent forms the frequency and duration of the various spontaneous remissions should be described. It has been established by observations to date that acute symptoms are more quickly and thoroughly relieved by insulin therapy than chronic symptoms. If one includes cases of the intermittent form associated with changes in character between the psychotic episodes, it is desirable to describe both the development of these changes and the nature and extent of their response to therapy.

Experience up to now has shown that the response to insulin treatment stands in inverse ratio to the duration of the illness. The shorter the duration the more certain the success of treatment. It is essential to determine the exact time when the schizophrenic disease process began. For this purpose, we regard the time of appearance of the earliest schizophrenic symptom in the patient's history as the onset of the illness. Since there is considerable difference of opinion as to what constitutes an essentially schizophrenic symptom, it is desirable in cases

of the borderline type in which the onset is insidious to describe briefly the beginning of the disease process. The following grouping employed by Max Müller is recommended:

Group 1: Duration of illness up to one-half year.

Group 2: Duration of illness up to one year.

Group 3: Duration of illness up to one and one-half years.

Group 4: Duration of illness over one and one-half years.

It is of course important, even in chronic forms, to indicate the duration of illness in terms of years.

PHYSICAL EXAMINATION

Each patient should be given a complete physical examination before the insulin treatment is started. Since knowledge of contraindications for the treatment is still incomplete, we believe that, for the present, all psychotic patients with severe physical symptoms should be excluded from treatment. Electrocardiographic studies before and during treatment are of particular significance (Müller). Complications involving diseases which existed before the beginning of treatment tend to distort the true figures for mortality resulting from the treatment.

THE TREATMENT

BRAND OF INSULIN

Commercial preparations of insulin are purified extracts of the pancreas prepared as a solution in various ways by different manufacturers. The preparation is tested only biologically, by ascertaining the drop in the level of blood sugar following the injection of small doses. The comparative potency of various preparations when used in large doses for a sustained period can be estimated only by actual clinical observation. It is therefore advisable when evaluating results to use only brands of insulin reported to have already been used in the treatment of schizophrenia. If new brands are used, they should be checked against the other brands in a series of control cases. The use of a new brand of insulin should always be mentioned specifically.

THE SYMPTOMS

The symptoms of shock may conveniently be classified under four syndromes:

I. *The Vegetative Vasomotor Syndrome in Wet Shock.*[2]—There are: 1. Changes in pulse rate. The rate was increased temporarily in 32.7 per cent of cases and diminished in 15 per cent. Marked fluctuations

2. My co-workers and I ascertained the percentages by tabulation of the results in 1,000 cases of shock.

occurred in 14 per cent. The behavior of the pulse is an indication, on the one hand, of the self-regulatory activity of the endocrine system and, on the other, of the condition of the heart and vascular system.

2. Progressive drop in temperature. The temperature shows a tendency to fall in all cases of wet shock. The temperature ranged from 35.5 to 33 C. (95.9 to 91.4 F.) in 5.5 per cent of cases and from 32 to 30 C. (89.6 to 86 F.) in 2.7 per cent of all cases of coma. In spite of the typical behavior of the temperature curve, the temperature gives no correct indication of the duration or depth of coma. Although the temperature tends to fall progressively throughout the duration of coma, the degree of the fall of temperature varies in different persons.

3. Perspiration and salivation. These occurred in 88 per cent of cases.

4. Vasomotor disturbances, such as pallor or flushing, without apparent correlation to type of shock (coma or seizure).

5. Fluctuations (usually a rise) in blood pressure.

II. *The Motor Syndrome.*—A. Convulsion Syndrome in Dry Shock.

1. Early epileptic seizure in so-called dry shock (before the end of the third hour after injection). This frequently occurs without perspiration. The sequence of events is: (*a*) pallor and rapid pulse; (*b*) cry; (*c*) conjugate deviation of the head and eyes (more frequently to the right); (*d*) tonic spasms followed by tonic-clonic spasms of epileptic type; (*e*) cyanosis, and (*f*) frequently a spontaneous Babinski sign.

2. Late epileptic seizure, occurring three hours after the injection—usually during coma. These seizures have manifestations similar to those described in 1, but with a preponderance of tonic features. Since they are due to a state of irritation produced by protracted hypoglycemia, these seizures have a tendency to repeat themselves.

B. Motor Syndrome in Wet Shock.[3] The following motor disturbances occur successively:

1. Motor restlessness and tremor.

2. Mild hypotonia.

3. Clonic twitchings; anomalies of tonic reflexes and coordination; fascicular, choreic and myoclonic twitchings; primitive movements, forced grasping; pathologic reflexes (e. g., the Babinski sign), and generalized torsion cramps, spasms and attacks of tremor.

4. Disappearance of forced grasping or spontaneous movement; dissociated torsion cramps.

5. Diminution in muscle tone and reflex activity; disappearance of defense reactions and the pathologic reflexes.

3. The description of the motor symptoms follows that of Angyal.

6. Areflexia; adduction or pronation of the extremities; contracture of the fists.

III. *Disturbances of Consciousness.*—A. Syndrome of Disturbances of Consciousness in Dry Shock.

1. Unconsciousness during and for a short time following an epileptic convulsion (early seizure).

2. Clouding of consciousness for a short time before full recovery of consciousness.

B. Syndrome of Disturbances of Consciousness in Wet Shock (Coma). The disturbances of consciousness are also dependent on the progress and duration of hypoglycemia. One observes in succession:[4] (1) somnolence; (2) sleep (the patient can be aroused); (3) incipient coma (the patient cannot be aroused when called); (4) sopor (deep sleep from which the patient can still be aroused by certain strong stimuli), and (5) coma. Coma is a condition of deepest sopor from which the patient can no longer be aroused by any stimulus. In cases in which the blinking and corneal reflexes have disappeared and a Babinski sign is also present, one can already speak of deep coma.

IV. *The Mental Syndrome.*—Mental disturbances are observed in the course of shock and after awakening. Early in hypoglycemia one often observes: increased activity; excitement and psychomotor restlessness, and, as signs of improvement, increased accessibility, better emotional rapport and more composed behavior. There is a reactivation of previous psychotic experiences (Sakel), or sometimes episodes of extreme excitement. These often occur again after termination of the hypoglycemia.

DOSAGE

The treatment consists essentially of the production of severe insulin coma of a certain duration and intensity, in the case of wet shock, or of epileptic seizures, in the case of dry shock. The duration and depth of coma vary with the dose of insulin and with the sensitivity of the patient (Müller); the reaction is dependent partly on the general endocrine balance of the patient and partly on metabolic conditions and other unknown factors. In general the shock dose is established in such a way that deep coma or an epileptic convulsion develops in two or three hours and threatening symptoms not earlier than four and a half hours after the injection. The maximum dose and maximum duration of hypoglycemia are determined, first, by the appearance of alarming symptoms and, second, by special therapeutic indications (see section on "variations depending on the size of the dose," p. 226).

4. This description is based on the observations of Dussik and Freudenberg.

TECHNIC

The injection of insulin is always given when the patient is fasting, as early in the morning as possible (from 6:30 to 7:30 a. m.). Treatment is started with small doses, which are increased until the desired shock reaction is obtained. This therapeutic dose is then maintained as long as the same effect is desired. When the symptoms have disappeared or it is concluded that the patient is resistant to further treatment, therapy is ended, usually by reduction of the doses. After a succession of several shocks, one or more days of rest are allowed to intervene. Accordingly, the treatment is divided into: the introductory phase (phase I according to Sakel); the phase of severe shock (phase II); the phase of rest (phase III), and the terminal phase (phase IV).

Introductory Phase.—One usually starts with from 10 to 20 units of insulin and increases the dose gradually until the signs of severe shock appear.

The increase in the dose of insulin may be 5, 10, 15 or 20 units a day and is partially dependent on the rapidity with which the symptoms of severe shock appear. The precise procedure is a matter of experience. The beginner should be warned against too rapid an increase in the doses, since symptoms of collapse or of protracted shock may ensue.

The duration of the introductory phase is dependent on the patient's particular sensitivity (Müller). Insulin shock may start in some cases with 40 (or in exceptional cases with 20) units of insulin. The number of days of treatment in the introductory phase varies in individual cases and is dependent on the rapidity of the increase in dose (slow or sudden) and on the size of the final dose required to produce shock.

Phase of Shock.[5]—The dose of insulin is regarded as adequate when shock is attained (consisting either of coma of sufficient depth or of an epileptic seizure). The duration of hypoglycemia depends on the patient's general condition, the quality of the pulse and the general

5. It should again be emphasized that these directions have essentially a practical and methodical use and should serve to standardize the technic. It must, of course, be recognized that during treatment all the other symptoms (pulse, temperature, mental changes, choreic twitchings and torsion spasms) should be considered. Similarly, the entire clinical course of improvement, the attitude of the patient and the like, must be taken into account. The symptoms enumerated here are merely indicative of different periods in the development of shock. They should serve for general orientation for purposes of description and for a quantitative analysis of the shock. These criteria are descriptive points of orientation which are meant to clarify the situation, though in actuality there are no sharp divisions between superficial and deep coma. At times certain of these symptoms may not appear at all or may be present in superficial form.

vascular response, as well as the severity of the motor symptoms, and should ordinarily not be protracted beyond four and a half to five and a half hours.

The beginning of shock is characterized by the following symptoms: (1) appearance of motor disturbances (such as clonic spasms) and epileptic convulsions in the second or third hour, in case of dry shock, and (2) loss of contact with the outside world (calling or touching), in case of wet shock.

Since clonic-tonic convulsions represent a marked reaction of the central nervous system (Angyal), either one of these reaction types suffices to indicate the onset of shock. It should be remembered, however, that in indicating the point at which severe shock begins one is interested mainly in having a standard for comparison and not so much in establishing or describing a clinical state.

The depth of coma usually varies progressively with its duration. The following successive changes are indicative of the progressive depth of coma: (1) appearance of the pathologic reflexes; (2) disappearance of the defense reactions, primitive movements and all spontaneous movement; (3) disappearance of the tendon reflexes; (4) disappearance of the pathologic reflexes, and (5) final general hypotonia. If hypoglycemia is not duly terminated, dangerous "late" seizures or toxic spasms may supervene.

These symptoms may also appear separately or in groups, and coincidentally or in succession. The therapeutic aim is to find a shock dose which will produce signs of dry shock with epileptic convulsion approximately in the second or third hour after the injection or wet shock in from the third to the fifth hour.

All the symptoms of deep shock need not be present. It is believed that the shock has reached a depth sufficient for therapeutic effect when one of the symptoms described has appeared. In many cases intense shock is not essential to therapeutic effect.

Termination of Hypoglycemia.—The therapeutic termination is ordinarily effected by feeding with a nasal tube sugar dissolved in water or, if the patient is in a poor state of nutrition, in milk. Ordinarily, a 40 per cent solution containing somewhat more than 1 Gm. of sugar per unit of insulin is used. If the patient habitually refuses nourishment the usual formula is used. The tube may be inserted prophylactically early in coma, to save time if quick tube feeding should be indicated later.

General Indications for Therapeutic Termination: 1. Intense shock: When intense shock has developed, as already described, hypoglycemia is terminated by tube feeding. This may be either after an early epileptic seizure or during wet shock—usually from four and a half to five and

a half hours after the injection, depending on the quality of pulse and respiration and the general reaction of the patient.

2. Appearance of generalized and *sustained* tonic extensor spasms. It should be remarked that transitory extensor spasms may also appear early in the course of hypoglycemia. The indication for termination, however, is given when sustained extensor spasms appear after the final hypotonic phase of shock, after the clonic components have subsided.

3. Sustained increase of the pulse rate to more than 120 a minute. Fluctuations in rate of the pulse or respiration in the course of hypoglycemic shock are usually transitory and disappear without intervention. The appearance, however, of an increase in the rate from four and a half to five and a half hours after the injection, or, in other words, during the final phase of hypotonia or extensor spasm, is particularly important. It should be regarded as a sign of bulbar involvement (Angyal), and it constitutes an absolute indication for termination.

In my opinion, these late fluctuations in pulse rate have a special character: The rate suddenly increases to from 120 to 160 a minute, and within a few seconds drops again to from 60 to 80; it then, in one or several minutes, rises again. Termination is especially indicated when the fluctuations in pulse rate occur during the tonic extensor spasms and are associated with respiratory disturbances (dyspnea, cyanosis and *Nasenflügel* respiration).

Special Therapeutic Indications for Termination: 1. Procedure in cases of catatonic stupor: Sakel has recommended that in certain cases of catatonic stupor shock should be terminated at the time when the patient shows greatest activity, consisting either of motor excitement or of reactivation of psychotic experiences. These psychomotor signs generally appear in about the second or third hour after injection of insulin. A reactivation of this sort can also be provoked by the intravenous (Meduna) injection of metrazol in the second or third hour of hypoglycemia (Georgi). When the stupor is broken and hebephrenic or paranoid symptoms become manifest, treatment can be continued according to the general scheme. In conditions of excitement, Sakel recommends termination of the hypoglycemia at the point of maximum pacification, before deep coma develops.

2. Variations depending on the size of the dose of insulin: If the dose is too small, the various signs of deep shock appear late and the hypoglycemic period may be extended to six or six and a half hours. If the dose is too large, the symptoms occur precipitately and the tonic extensor spasms appear in the third or fourth hour.

If the dose is too large or the hypoglycemia is too prolonged (over five hours), threatening phenomena occur. The signs of precipitate or protracted shock are: (*a*) sustained tonic extensor spasms; (*b*)

the Kussmaul type of respiration; (*c*) the Cheyne-Stokes syndrome; (*d*) rapid, irregular, thready pulse, and (*e*) sudden vascular collapse.

Intervention in cases of precipitate or protracted shock is discussed later.

Sensitization: In the course of treatment the patient may become sensitized to insulin (Müller), and the same dose may produce either a superficial reaction or precipitate shock. When sensitization is noted, the dose must be readjusted.

Number of Severe Shocks: Treatment with severe shock is continued [6] until the desired therapeutic result is achieved. The treatment is sufficiently successful when (*a*) the patient is recovered and (*b*) psychotic phenomena no longer occur in the course of hypoglycemia.

According to our experience to date, the maximum number of severe shocks at present is considered to be about fifty. If the patient has not then shown improvement, he is to be discharged from treatment as "unimproved." Complete recovery, however, often occurs after much fewer than fifty shocks.

In cases, however, in which no marked improvement has occurred but in which the prognosis seems favorable, the maximum number of shocks may be exceeded. Our recommendations regarding the duration of treatment have no theoretical basis.

Rest Days and the Final Phase.—At least every seventh day is one of rest. It is occasionally desirable, however, to give small doses of insulin (from 20 to 30 units) even on rest days, to cover the carbohydrate requirements of the day.

When the treatment achieves a successful result, or when fifty shocks or more are produced without results, treatment is tapered off by reducing the dose by from 20 to 40 units a day. In some cases this final phase may be omitted. After careful examination of the patient's condition, treatment is then concluded.

DANGERS OF INSULIN SHOCK AND INDICATIONS FOR IMMEDIATE INTERVENTION

In the course of shock symptoms may appear which indicate danger to the patient's life and require immediate intervention. According to the degree of danger, one may distinguish: (1) indications for early termination by feeding with the stomach tube and (2) indications for rapid termination by intravenous injection (vital indication).

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6. The relation between the various intensities of shock and the degree of recovery is still more or less indefinite, and can finally be determined only by treating large parallel series of patients with shock of different degrees of intensity and duration and by comparing the therapeutic results (Sakel, Manfred: Pharmacological Shock Treatment of Psychoses, New York, 1938).

Early Termination by Tube Feeding.—Hypoglycemia is terminated early when threatening signs are observed or when the continuation of shock is no longer indicated for therapeutic reasons. The indications for early termination are: (1) prolonged inspiratory dyspnea with moderate cyanosis (*Nasenflügel* respiration); (2) irregular, soft pulse, pallor and respiratory distress, and (3) early appearance of sustained extensor spasms associated with moderately good cardiac and vascular function.

Sakel enumerated the following psychiatric indications for early termination: (1) "hunger row" and (2) sudden, spontaneous awakening in the fifth hour after injection of insulin. In case of the latter the solution of sugar can often be administered by mouth.

Early termination may of course become advisable at any time during hypoglycemia. The most important consideration involved in early termination by tube feeding is the conviction that the patient's condition is only "moderately" threatening.

Rapid Intravenous Termination by Injection of Dextrose.—Termination by intravenous injection is resorted to when actual danger to life is threatened or when the possibility of such danger arises. The following dangers may be involved in the course of shock:

1. Severe dyspnea or apnea (bulbar involvement, according to Angyal).

2. Protracted or precipitate shock with its consequences.

3. Cyanosis of the mucous membranes associated with rapid, soft and thready pulse.

4. Vascular collapse.

5. Late epileptic seizure (in the fourth or fifth hour).

6. Myoclonic vascular collapse. Other workers and I have described a type of seizure which we have designated as myoclonic vascular collapse. It is characterized by generalized rapid twitchings of myoclonic character, either preceded by signs of or associated with collapse.

7. Laryngospasm with signs of apnea.

Hypoglycemia is terminated by the intravenous injection of a sterile solution of from 25 to 33 per cent dextrose. On an average, up to 70 cc. of the solution of dextrose is given. In cases in which the patient does not awaken, larger quantities may be administered. In most cases the patient awakens during the first injection.

If the veins have collapsed and intravenous injection becomes difficult, an intramuscular injection of 0.1 per cent epinephrine may be given. Only in case of immediate danger of death should intracardiac injection be resorted to.

If the patient still cannot be aroused from the insulin shock, immediate spinal tap for decompression (15 cc.) is indicated, and venesection may be attempted. Infusion of solution of sodium chloride is often helpful. Oxygen inhalation is particularly valuable.

It is desirable to tabulate all instances in which early termination was necessary, with the indications and the method used, so that the frequency of the various indications can be determined and the efficacy of the different procedures compared. According to my experience, early termination is necessary in about 7 per cent of all cases of shock.

RECORDS

In order to allow a simple summary and comparison of the results of treatment with insulin, the following standard form for record of the main points in the treatment is recommended:

1. Successive case number.
2. Given name; family name; sex.
3. Age.
4. Duration of illness.
5. Diagnosis of the type of schizophrenia.
6. Date of the beginning of treatment.
7. Days of insulin treatment, i. e., the total number of days on which the patient received insulin.
8. Hours of insulin treatment, i. e., the total number of hours, from the time of injection to the time of termination.
9. Number of hours that patient was unconscious.
10. Number of severe shocks—(*a*) coma; (*b*) seizures.
11. Maximum single dose.
12. Date of conclusion of treatment.
13. Total amount of insulin used.
14. Degree of recovery.
15. Remarks.

DEGREE OF RECOVERY

The results are to be tabulated as follows: (1) complete recovery (+++); (2) incomplete recovery (++); (3) partial recovery (+), and (4) no improvement (—).

1. Four criteria for complete recovery as described by Müller are recommended for adoption: (*a*) complete disappearance of schizophrenic symptoms; (*b*) restoration of adequate emotional response; (*c*) critical insight into the past illness, and (*d*) full capacity for return to former work.

2. The patient is said to have recovered incompletely when any one of the preceding requirements is lacking.

Sample of System of Recording

Serial No.	Name	Age, Yr.	Duration of Illness	Type of Schizophrenia	Beginning of Treatment	Days of Treatment	Total Hours of Hypoglycemia	Total Hours of Unconsciousness	Number of Severe Shocks: Coma	Number of Severe Shocks: Seizures	Maximum Single Dose, Units	Total Amt. of Insulin Used, Units	End of Treatment	Degree of Improvement	Comments
A. Cases in Which Course of Illness Was Continuous															
1. Duration of Illness Up to Six Months															
1	L. R.	24	5 months	Catatonic	4/ 1/36	53	207	94	38	1	125	4,630	5/27/36	+++	
2	E. K.	22	5 months	Catatonic	4/28/36	60	171	68	31	0	150	6,080	7/10/36	+++	
3	H. S.	18	6 months	Hebephrenic and catatonic features	5/24/36	50	170	51	30	4	120	3,730	5/14/36	+++	
2. Duration of Illness Up to One Year															
1	I. F.	26	9 months	Paranoid	2/25/36	25	100	5	7	0	180	2,430	3/21/36	+++	Relapsed 9/21/36
2	I. R.	40	12 months	Paranoid	3/17/36	33	116	20	17	0	120	2,010	4/19/36	++	
3	K. K.	26	12 months	Paranoid	6/29/36	83	278	65	55	1	190	9,780	10/ 5/36	++	
3. Duration of Illness Up to One and a Half Years															
1	M. K.	45	14 months	Paranoid with depressive features	8/17/36	75	248	75	45	0	170	8,765	11/15/36	—	
2	R. I.	36	14 months	Catatonic stupor	5/ 4/36	23	80	12	14	0	100	1,740	5/27/36	—	Treatment discontinued because of exacerbation of endocarditis
4. Duration of Illness More Than One and a Half Years															
1	N. R.	26	19 months	Paranoid	6/ 8/36	39	128	46	26	0	110	2,805	7/17/36	—	
2	F. G.	34	27 months	Hebephrenic-catatonic features	6/15/36	59	155	26	23	0	110	3,600	8/16/36	+++	
3	R. D.	20	4 years	Catatonic stupor	6/12/36	55	167	54	44	2	150	4,980	8/ 5/36	+++	
4	W. L.	36	10 years	Chronic paranoid features without deterioration	5/ 8/36	38	128	5	5	0	170	3,190	6/24/36	+	
B. Cases in Which Course of Illness Was Intermittent															
1	F. K.	33	Two episodes within 2 years, lasting on average 3 mo.	Catatonic with manic features; character changes in intervals	6/12/36	56	210	62	38	6	160	6,520	8/ 9/36	+++	Disappearance of character defects
2	C. F.	33	Seven episodes within 17 yr., lasting average of 3.4 mo.	Mixed psychosis—predominantly hebephrenic-catatonic features; character defects in intervals	7/12/36	16	58	13	8	0	80	850	7/28/36	+++	Disappearance of character defects

3. The term partial recovery is applied in cases in which certain of the symptoms have disappeared or in which the patient shows partial improvement (e. g., pacification, social behavior and capacity for work of an autistic, unstable patient).

CONCLUSION

Close observance of the aforementioned rules or exact information on variations from Sakel's procedure can do much to solve the problem of the pharmacologic shock treatment. Unfortunate misunderstandings involved in a trial of this therapy can be avoided and the way cleared for a systematic, progressive solution of the many problems.

PROTAMINE ZINC INSULIN

ITS UNSUITABILITY FOR HYPOGLYCEMIC SHOCK THERAPY

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Various reports from Europe have attested to the success of insulin shock therapy in early stages of schizophrenia. The Vienna school, where the method was introduced by Sakel [1] in October 1933, has treated well over 200 patients by now, and a report of the first 104 cases has been published in detail by Dussik and Sakel.[2] Their figures show that of cases in which psychotic symptoms had existed for less than six months they secured perfect remissions (no demonstrable mental abnormality on discharge) in 73 per cent and social remissions in 12 per cent, making a total of 85 per cent in which the patients were able to return to work. Independent investigators, among whom were Glueck [3] and Wortis,[4] in the United States, and Strecker [5] and Wilson [6] in England, observed the administration of treatment in some cases in this series and interviewed many of the former patients; these authors have confirmed the results achieved. Furthermore, the Swiss experience, as reported by Müller [7] embraced 118 cases in which there was a strikingly similar percentage of remissions—complete in 76 per cent and social in 85 per cent of cases in which the duration was less than six months, and complete in 53 per cent and social in 82 per cent of cases in which the duration was from six to eighteen months. When applied to conditions of longer standing than eighteen months, this

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method of therapy has met with only occasional success. A few patients with remissions have had relapses, but usually when treatment was insufficient. In any event, the percentage of relapses reported has been small—about 10. Comparison of the preceding figures and those for spontaneous remissions in schizophrenia (from 10 to 20 per cent) can leave no doubt as to the significance of this new treatment. The best reviews on the subject are the monographs by Sakel [8] and Wilson.[6]

The method is not without difficulties and dangers, however, and Sakel [9] has expressed the hope that some way may be found to lessen the danger of severe individual reactions without impairing the beneficial effect.

After we had become familiar with the reactivity of our patients to old insulin and had learned to evaluate the signs and symptoms of hypoglycemia, it occurred to us that protamine zinc insulin might furnish a better therapeutic medium than regular insulin, by virtue of its special properties. The peculiar effects of the new insulin have been discussed by Hagedorn,[10] Root,[11] Wilder [12] and Joslin [13] and their associates (among others) and consist in: (*a*) prolonged action—from twenty-four to forty-eight or more hours—because of its slow absorption; (*b*) a slow fall in blood sugar, and (*c*) infrequent and mild hypoglycemic reactions. All writers have emphasized that the full effects may not appear for four or five days.

The efficacy of insulin shock therapy appears to depend in general on the depth of shock achieved, which, in turn, is roughly proportional to the extent of the fall in blood sugar. Deep comatose shock is usually not allowed to last for more than two or three hours, and not infrequently this period has to be shortened because of the appearance of alarming symptoms (weak or irregular pulse, Cheyne-Stokes respiration, cyanosis or pallor, aspiration of saliva, muscular twitchings, convulsions or hunger and thirst excitement). We hoped that the slow action of protamine zinc insulin might enable us to induce and maintain long-continued hypoglycemic states of high therapeutic effect minus

8. Sakel, Manfred: Neue Behandlungsmethode der Schizophrenie, Vienna, Verlag M. Perles, 1935. This monograph is a reprint of the articles listed in footnote 1.

9. Sakel,[8] page 111.

10. Hagedorn, H. C.; Norman Jensen, B.; Krarup, N. B., and Wodstrup, I.: Protamine Insulinate, J. A. M. A. **106**:177-180 (Jan. 18) 1936.

11. Root, H. F.; White, P.; Marble, A., and Stotz, E. H.: Clinical Experience with Protamine Insulinate, J. A. M. A. **106**:180-183 (Jan. 18) 1936.

12. (*a*) Sprague, R. G.; Blum, B. B.; Osterberg, A. E.; Kepler, E. J., and Wilder, R. M.: Clinical Observations with Insulin Protamine Compound, J. A. M. A. **106**:1701-1705 (May 16) 1936. (*b*) Wilder, R. M.: Minnesota Med. **20**:6-15 (Jan.) 1937.

13. Joslin, E. P.; Root, H. F.; Marble, A.; White, P.; Joslin, A. P., and Lynch, G. W.: New England J. Med. **214**:1079-1086 (May 28) 1936.

some or all of this dramatic symptomatology. We abandoned our method of procedure after a month and returned to the use of regular insulin, for reasons which will be detailed later. Our results are of interest in that they represent, to our knowledge, the first studies showing the effect of repeated large doses of protamine zinc insulin on the levels of the blood sugar in biochemically (though not biologically) relatively normal persons. The product used was a protamine zinc insulin compound [14] and was furnished by Dr. Elmer Sevringhaus, of the University of Wisconsin Medical School.

METHOD

Nine patients with unquestionable schizophrenia were treated for more than a month. Each of them received from thirteen to nineteen intramuscular injections of protamine zinc insulin. It was our desire to administer treatment daily, but various circumstances, chiefly difficulties in supervision and laboratory facilities, made several gaps in treatment unavoidable. One dose of protamine zinc insulin was given per day, at 7 or 9 a. m.; occasionally two doses were employed. The patients received no breakfast on treatment days; the other two meals were ample, and extra carbohydrate, in the form of malted milks, ice-cream and sugar water, was often given in the afternoon, with the evening meal and sometimes during the night. The insulin dose was begun with 40 units daily in most cases and was raised in steps of 10 units. Most of the patients received a maximum dose of 120 units, but this was continued for only two or three days. Estimations of the blood sugar were made daily prior to administration of insulin and before termination of the shock, with more frequent determinations on several days. Four of the patients were regarded as unsuitable for therapy because of the long duration of symptoms. The results are summarized in the table.

COMMENT

When single, moderately large doses of regular insulin are administered to a patient on successive mornings, breakfast being omitted, the blood sugar reacts as shown in chart 1 *B*. From an initial fasting value, which lies within fairly circumscribed limits (from 80 to 92 mg. per hundred cubic centimeters in this instance), the level drops after from one-half to three hours to a low point, which is then maintained for several hours if no food is given; thereafter, there is a gradual rise to normal, whether food is given or not. We did not keep our patients without food for more than seven hours after the injection, during which time serial studies on the blood revealed little tendency for the sugar to rise (with either regular or protamine zinc insulin). Wilder and his co-workers [12a] published a chart showing recovery of the original value in twelve hours (data were obtained from a fasting patient with diabetes after administration of regular insulin). At all events, when old insulin is used, the blood sugar has returned to its usual fasting

14. The protamine zinc insulin was obtained from Eli Lilly and Company, Indianapolis.

Data on 9 Patients Who Were Treated with Protamine Zinc Insulin

Case; Sex; Age, Yr.	Diagnosis	Duration of Illness	Education	Symptoms	Results
1. E. K. F 35	Paranoid schizophrenia	8 yr.	M.A. degree	Suicidal attempts; difficulty in thinking and understanding; paranoid ideas; irritability; tension; periodic excitement; assaultiveness	Questionable improvement
2. M. L. F 40	Paranoid schizophrenia	2 yr.	Nurse	Bizarre delusions; auditory hallucinations; ideas of influence; "sphymeograph" records her thoughts, as does any clock	No improvement
3. C. O. M 27	Paranoid schizophrenia	1 yr.	Eighth grade	Ideas of influence, hypnosis, mind being read and poisoning; suspiciousness; double thought; vague auditory hallucinations	Improvement
4. G. T. M 25	Paranoid schizophrenia	10 mo.	Ph.D. degree	Inability to concentrate, headache, "bad dreams," confusion, ideas of reference and delusions of poisoning and influence; tied up mouth at night because enemies made him talk in his sleep	Social remission
5. A. E. M 19	Hebephrenic schizophrenia	3 mo.	High school	Vague ideas of reference and poisoning; auditory and visual hallucinations; apathy; inappropriate smiles; semimutism	Improvement
6. G. B. M 30	Hebephrenic schizophrenia	3 yr.	B.A. degree	Bizarre delusions (he is George Washington); visual and auditory hallucinations; ideas of influence and mind-reading; apathy; semimutism	No improvement
7. G. S. M 18	Catatonic schizophrenia	6 mo.	High school	Delusions of venereal disease; auditory hallucinations; mutism; refusal of food (tube fed); muscular tension	No improvement
8. H. A. M 23	Catatonic schizophrenia	5 yr.	Eighth grade	Slow mentality; change in personality; seclusiveness; enuresis; worry over masturbation; slow movements and responses; fetal posture; vasomotor changes in legs	Social remission
9. L. B. M 22	Hebephrenic schizophrenia	8 mo.	High school	Somatic complaints; insomnia; delusions of grandeur (he is the world's greatest actor, could be the greatest physician, scientist, etc.); inappropriate affect and manner; change of character; intelligence quotient 111	Improvement

value by the morning after the injection. This cycle may be repeated daily for weeks or months.

With protamine zinc insulin, when approximately the same dosage and technic are used, the results are different (chart 1 *A*). When the effects of the new insulin and those produced by equal doses of regular insulin are compared, one sees that with protamine zinc insulin the initial lowering of blood sugar is a little less and the rate of fall some-

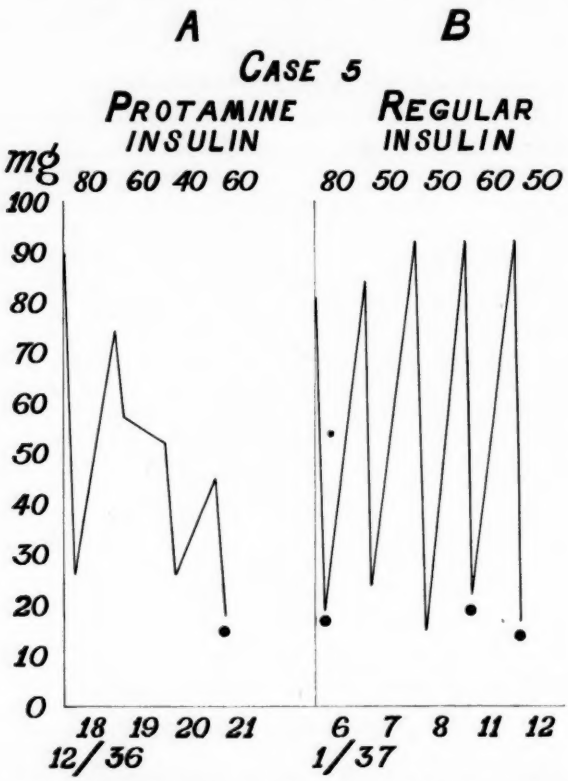

Chart 1.—Effects on the blood sugar of repeated daily doses of protamine zinc insulin (*A*) and regular insulin (*B*). Note the fairly constant level at which the morning (fasting) blood sugar remains with regular insulin, whereas with the protamine compound there is a steady fall. The dots indicate convulsive episodes which occurred with unusual frequency in this patient.

what slower. A striking contrast appears, however, in the effect on successive morning (fasting) levels of blood sugar, which, owing to the prolonged activity of the protamine compound, show a steady decline, until in three or four days low levels (from 30 to 40 mg. per hundred cubic centimeters) are reached. At this stage the patient may show hypoglycemia for twelve hours at a stretch. This "protamine

hang-over effect" is illustrated in chart 1 *A*. To emphasize further the comparison with regular insulin, the values for the morning sugars only in chart 1 *A* and *B* were replotted in chart 2. With regular insulin this curve is fairly flat; with protamine zinc insulin the steady decline is evident. Chart 3, showing the course of the curve for blood sugar in one patient throughout treatment, furnishes several examples of the same phenomenon.

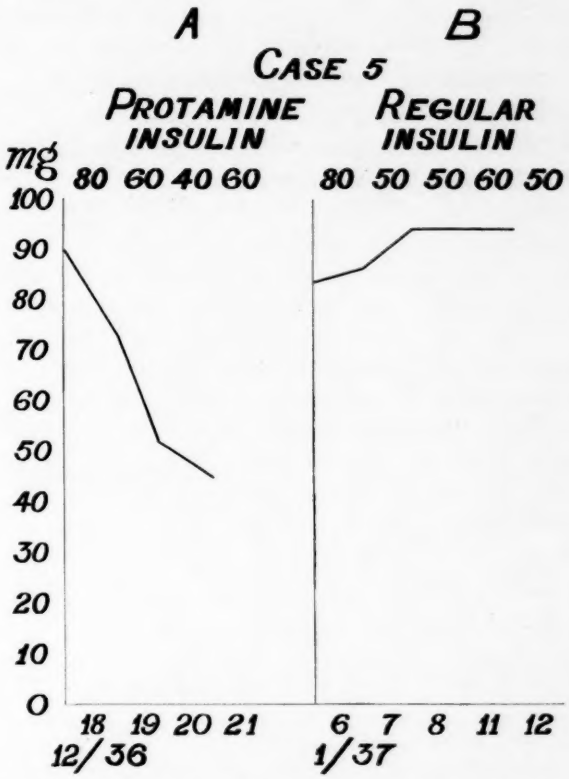

Chart 2.—The values for the morning sugar only in chart 1 have been replotted here. The curve for the "protamine hang-over effect" (*A*) contrasts sharply with the relatively flat curve obtained with regular insulin (*B*).

A further contrast between the effects of protamine zinc insulin and those of regular insulin appears in the type of shock produced. When a "shock dose" of regular insulin is administered, the various manifestations of insulin shock occur in well known orderly sequence. In one or two hours the subject sweats slightly and feels hungry. He then becomes confused; his speech is thick, his visual fixation poor and his gait unsteady; in a word, he acts as though "drunk." One or two hours later the subject falls into coma, of varying depth. Profuse, beady

sweat and excessive salivation usually complete the picture of this comatose "wet" type of shock.

When protamine zinc insulin is used, this orderly sequence of events is rare. It is difficult—indeed, almost impossible—to produce comatose shock, even with large doses of the protamine compound and blood sugar levels comparable with the lowest obtained with regular insulin. All our patients received doses of protamine zinc insulin up to 120 units on successive days, and comatose shock was a rarity, even with blood sugar levels of from 18 to 20 mg. The same lack of reaction may occur with regular insulin, but infrequently; when the blood sugar falls

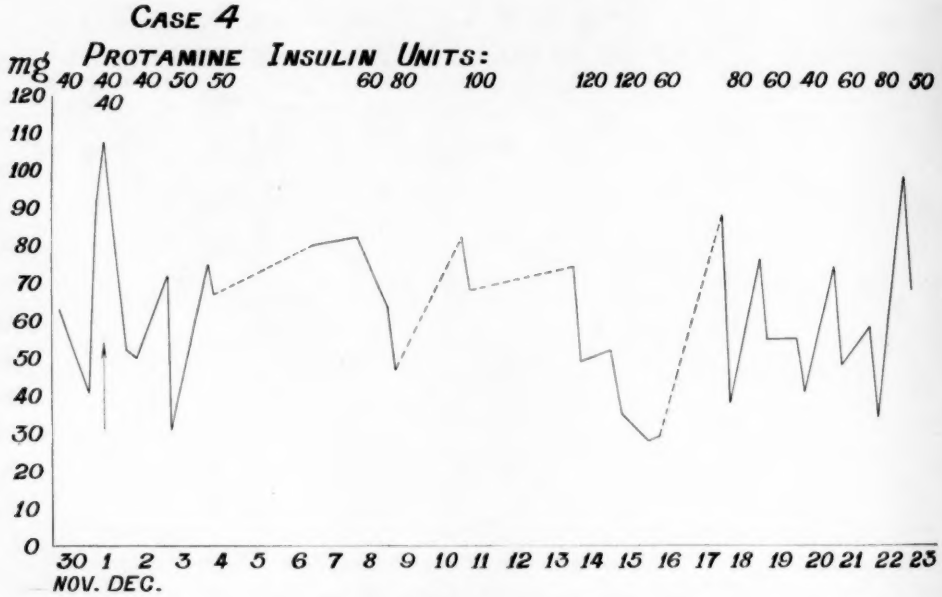

Chart 3.—Course of the blood sugar throughout treatment in case 4. Several examples of the "protamine hang-over effect" are shown, while a mild "paradoxical response" (a rise instead of a drop in sugar following administration of insulin) appears above the arrow. The broken lines indicate gaps in treatment.

below 30 mg. the patient is usually comatose. The deepest stage of shock usually attainable with protamine zinc insulin is light coma, from which the patient is easily aroused, and even this is rare. Often the only changes noted are hunger and sweating. Moreover, the whole effect of protamine zinc insulin is inconstant in our experience, equal doses producing effects of different magnitudes on various days. It was this variability of effect, together with some difficulties to be mentioned, which led us to abandon our researches with protamine zinc insulin and to use regular insulin instead.

DIFFICULTIES AND DANGERS

The progressive fall in morning levels of the blood sugar previously referred to as the "protamine hang-over effect," while a fairly constant phenomenon, is, unfortunately, not predictable for any given day or patient. The effect may be absent when small daily doses of from 40 to 50 units are used, and even with larger doses the blood sugar not infrequently escapes from the depressant influence and shoots up on the next morning to considerably higher levels. An example of this escape phenomenon appeared on December 22 in case 4 (chart 3). The patient was well "protaminized" and received 80 units at 7 a. m. The blood sugar fell only to rise again the next morning to the second highest level on the graph—in marked contrast to the "protamine hang-over effect," several instances of which appear on the chart. Variations in carbohydrate intake may account for this escape phenomenon, as the daily weighed diet of our patients was not constant, but we do not believe this to be so, since, if minor variations in heavy carbohydrate intake were of such significance, the "protamine effect" would never be demonstrable.

Moreover, we found that it was impossible for us to estimate the level of the blood sugar with protamine zinc insulin either early in the morning or during the day without actual laboratory determination (the result of which we could not learn until the next day). This fact made shock therapy with protamine zinc insulin a potentially hazardous and worrisome procedure for us. Like the proverbial gunner on the powder keg, we expected an explosion at any moment, and we often shuddered, as we read the reports on the sugar levels of the previous day, at the thought of the insulin doses we had given. That no complications worse than convulsions occurred in our patients is a tribute to the adaptive powers of the human organism.

With regular insulin one needs no immediate laboratory aid in carrying out shock therapy. The fasting (morning) sugar level lies within fairly well defined limits, and the next day's dose of insulin is determined by the reaction of the patient during hypoglycemia. Once the shock dose is established, it may be maintained unchanged for weeks. When protamine zinc insulin is used, however, close laboratory cooperation, with sugar determinations made during the day and night, is essential. No constant "shock dose" is to be found, the amount given varying from day to day.

A few other difficulties with protamine shock therapy are worthy of note. As already mentioned, it is possible to produce the desired comatose wet shock only seldom. If the blood sugar is lowered to "comatose" levels there appears to be more danger of the convulsive type of shock than when regular insulin is employed. Finally—and

this is perhaps the gravest objection to the use of protamine zinc insulin in shock therapy—the likelihood of secondary hypoglycemic shock, or "after-shock," is greatly increased, even when heavy meals are given. With regular insulin, secondary shock appearing several hours after feeding is a rarity, which we have not encountered. With the protamine zinc compound, the patients often complained of sweating, hunger and weakness at night, and 1 patient (case 5) once went into convulsions at 1 a. m.—a severe "after-shock."

The difficulties outlined led us to abandon our work with protamine zinc insulin. We feel more comfortable with the use of regular insulin, in which we can estimate the blood sugar level fairly closely and do not have to worry about nocturnal convulsions.

RESULTS OF TREATMENT

In 4 of the 9 patients treated the condition was classified as "old," with a duration varying from two to eight years, while in the rest the onset was recent, with symptoms for several months only. Of the patients with conditions of long standing (considered to present an unfavorable prognosis, even with treatment) 2 showed no change, 1 questionable improvement and 1 a good social remission. The last patient (case 8) had been catatonic for five years and in a mild stupor for one year. He was the only one of our patients to react consistently with deep shocks, which were terminated regularly after several hours because of clonic jactitations. At the conclusion of treatment, the catatonic features had disappeared entirely, and the patient's family considered him restored to normal. To us, he still appeared rather slow and dull, but this behavior may have been merely the manifestation of an underlying mental defect (he finished the eighth grade at the age of 16, and his intelligence quotient was 77). No psychic symptoms were present on discharge.

Of the 5 patients with conditions of recent onset, 1 showed no improvement, 3 moderate improvement and 1 a satisfactory social remission.

Two other points of interest may be mentioned in conclusion. Sakel [15] stated that in his experience it is almost impossible to lower the blood sugar below 40 mg. per hundred cubic centimeters, no matter how great the dose of insulin. In our cases, on the contrary, sugar readings below 30 mg. were common, and we have recorded figures of 20 mg. or below on 34 occasions. Our lowest sugar level was 14 mg. per hundred cubic centimeters. Differences in laboratory technic and regional variations in the blood may account for this discrepancy. Our

15. Sakel,[8] page 30.

sugar determinations were made by the colorimetric copper method of Folin and Wu on whole blood from the cubital vein.

Last, we shall refer briefly to a phenomenon that we call the "paradoxical sugar response." It may occur when either protamine zinc insulin or regular insulin is used, but it is rare in any event. We noted only 4 instances in 207 treatment days. In the "paradoxical sugar response," the blood sugar rises, rather than falls, after the injection of insulin. In one instance it rose from 77 to 306 mg. The patient's behavior appears to depend, however, as Sakel has reiterated, on the size of the insulin dose rather than on the level of the blood sugar. In 3 of the 4 instances in our experience, the dose given was the patient's shock dose, and the subjects reacted with deep coma despite the high values for blood sugar. There was no muscular irritability to account for the rise in sugar. Moreover, 5 Gm. of a 50 per cent solution of dextrose given intravenously restored the patients to consciousness. The hygroscopic action of the hypertonic solution may have been responsible for the arousal in these instances. A mild form of this reaction occurred on December 1 in case 4 and is illustrated in chart 3. The subject showed only moderate sweating—his usual reaction to a dose of similar size. This interesting, but unpredictable, phenomenon is worthy of further study.

CONCLUSIONS

1. Protamine zinc insulin is not suited to hypoglycemic shock therapy for schizophrenia because: (*a*) the effects of equal doses are not always the same; (*b*) the dose must be constantly varied, since no uniform shock dose can be established; (*c*) closer laboratory cooperation, with frequent determinations of the blood sugar, is required with this compound than with regular insulin; (*d*) the danger of after-shock is greater, and (*e*) epileptiform shocks are somewhat more frequent.

2. Shock therapy with protamine zinc insulin differs from that with regular insulin, since (*a*) with large doses the fasting (morning) sugar level declines steadily, and (*b*) it is almost impossible to produce comatose, wet shock.

3. The comatose phase of insulin shock depends on the rate of fall of the blood sugar, as well as on the level reached.

SUMMARY

Nine patients with schizophrenia were treated with protamine zinc insulin in daily amounts of from 40 to 120 units. The results are described, and the action of repeated large doses of protamine zinc insulin is contrasted with that of similar amounts of regular insulin.

The staff of the Mendota State Hospital cooperated and assisted in carrying out this study.

HYPOGLYCEMIA

NEUROLOGIC AND NEUROPATHOLOGIC STUDIES

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AND
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Chameleon-like, the bizarre nervous symptoms due to hypoglycemia may go unrecognized for long periods unless the physician is "hypoglycemia conscious." In 1934 Rynearson and one of us (F. P. M.) [1] and others, such as Sevringhaus,[2] Carr,[3] Bowen and Beck,[4] Tedstrom,[5] Wolf and his associates [6] and Corff,[7] pointed out that practically all patients with hypoglycemia have neurologic symptoms of one type or another. The fact remains, however, as suggested by Allan,[8] that hypoglycemic states are not common, and when they first present themselves, they are readily misinterpreted because of the circumstances surrounding their development.

From the Section on Neurology (Dr. Moersch) and the Section on Surgical Pathology (Dr. Kernohan), the Mayo Clinic.

Read before the Section of Nervous and Mental Diseases at the Eighty-Eighth Annual Meeting of the American Medical Association, Atlantic City, N. J., June 11, 1937.

1. Rynearson, E. H., and Moersch, F. P.: Neurologic Manifestations of Hyperinsulinism and Other Hypoglycemic States, J. A. M. A. **103**:1196-1199 (Oct. 20) 1934.

2. Sevringhaus, E. L.: Nervous and Mental Phenomena Accompanying Insulin Therapy, Arch. Neurol. & Psychiat. **22**:746-751 (Oct.) 1929.

3. Carr, A. D.: Neurologic Syndromes Associated with Hypoglycemia, J. A. M. A. **97**:1850-1852 (Dec. 19) 1931.

4. Bowen, B. D., and Beck, Gilbert: Insulin Hypoglycemia: Two Cases with Convulsions; One Necropsy Report, Ann. Int. Med. **6**:1412-1425 (May) 1933.

5. Tedstrom, M. K.: Hypoglycemia and Hyperinsulinism, Ann. Int. Med. **7**: 1013-1025 (Feb.) 1934.

6. Wolf, Abner; Hare, C. C., and Riggs, H. W.: Neurological Manifestations in Two Patients with Spontaneous Hypoglycemia, with Necropsy Report of Case of Pancreatic Island Adenomata, Bull. Neurol. Inst. New York **3**:232-251 (June) 1933.

7. Corff, Meyer: Hyperinsulinism, Am. J. Surg. **34**:241-247 (Nov.) 1936.

8. Allan, F. N.: The Diagnosis and Treatment of Hyperinsulinism, S. Clin. North America **15**:1481-1488 (Dec.) 1935.

With Sakel's [9] introduction of the insulin shock treatment for schizophrenia, an excellent opportunity was afforded for the study of the various neurologic and psychiatric manifestations occurring during the hypoglycemic state. Thus, it is now well recognized that there is no single syndrome that is pathognomonic of hypoglycemia; as Tedstrom [5] stated, hypoglycemia is not a disease entity but a symptom complex which is defined by deficiency in blood sugar.

The symptoms of hypoglycemia are endless and cover the entire range of neurologic and psychiatric manifestations. It is true that in a given case there is a tendency for the symptoms to follow a certain pattern from one attack to another; such a rule is not constant, however, and striking variations may occur.

In forty-four selected cases of hypoglycemia we have been able to observe the effects of about five hundred severe hypoglycemic reactions. These cases were classified on the following basis: spontaneous hypoglycemia, twelve cases; hyperinsulinism, nine cases; insulin-induced hypoglycemia in patients with diabetes, eight cases; hepatogenic hypoglycemia, two cases, and induced hypoglycemia in schizophrenia, thirteen cases. From the standpoint of the neurologist the cardinal features of the hypoglycemic attack are: (1) the periodic occurrence of transitory episodes of a neurologic or psychiatric character; (2) the apparent absence of the usual neurologic or psychiatric causes to explain the symptoms, which may be mild, bizarre or violent; (3) the occurrence of the attack at periods of hunger or marked exertion; (4) the tendency for the attacks to appear in the third and fourth decades of life, except in the group of cases in which the condition is induced by insulin therapy; (5) the tendency for many of the patients to gain weight; (6) the usual feeling of well-being between attacks; (7) the presence of a low fasting value for blood sugar, and (8) the usual complete recovery from an attack on treatment with dextrose.

Many authors have attempted to divide the symptoms of hypoglycemia into various stages: Bowen, for example, has divided them into two stages and Wauchope [10] into five. Harris,[11] on the other hand, spoke of mild, severe and very severe attacks of hypoglycemia, while

9. Sakel, M.: Schizophreniebehandlung mittels Insulin-Hypoglykämie sowie hypoglykämischen Schocks, Wien. med. Wchnschr. **84**:1211 (Nov. 3); 1265 (Nov. 17); 1299 (Nov. 24); 1326 (Dec. 1); 1353 (Dec. 8); 1383 (Dec. 15); 1401 (Dec. 22) 1934; **85**:35 (Jan. 5); 68 (Jan. 12); 94 (Jan. 19); 121 (Jan. 26); 152 (Feb. 2); 179 (Feb. 9) 1935.

10. Wauchope, G. M.: Hypoglycaemia: A Critical Review, Quart. J. Med. **2**:117-156 (Jan.) 1933.

11. Harris, Seale: Clinical Types of Hyperinsulinism: Report of Cases, Am. J. Digest. Dis. & Nutrition **1**:562-569 (Oct.) 1934.

Unverricht [12] emphasized the transitory nature of the symptoms. These divisions and classifications are more or less arbitrary since one stage may merge imperceptibly into another and the severity of the attacks may vary in the same patient. For our purpose we may say that there are four rather definite stages through which the patient passes in the typically severe hypoglycemic attack, whether induced or of endogenous character. The length of the hypoglycemic attack varies, and it may terminate spontaneously or under treatment at any point in its course.

The usual sequence of events in hypoglycemic attacks is as follows: First, there is the prodromal stage. This is a period of from about ten to thirty minutes, in which the patient rather rapidly becomes mentally and physically retarded but is rarely agitated. There is increasing lassitude, with beginning pallor and mild mental confusion. During this period irritability, restlessness, transitory diplopia and increasing confusion may be present. The blood pressure remains fairly constant or falls slightly. The pulse rate and respirations are unaltered. The blood sugar may be but slightly altered, although a low value may be present in this stage. In cases of induced hypoglycemia drowsiness is the outstanding symptom of this stage. During this period the attack may subside, and the patient may regain his normal feeling of "well-being." Such an attack, according to Harris, is mild. More often the symptoms progress rapidly in one of two directions, and the second stage is reached.

The second stage is that of confusion and stimulation. There is now increasing pallor; profuse perspiration appears; the patient becomes restless; his confusion increases; he may act as if drunk, and he gradually sinks into stupor or coma, with or without convulsive phenomena. On the other hand, the symptoms may be quite the reverse. In place of progressive apathy and stupor there may be increasing excitement and agitation; somnambulism or fugue states may appear, and delirium or mania may be present, which usually give way to stupor or coma. It is in this second stage that the convulsive manifestations may appear, although they may not be present until the stage of coma. During this second stage, and more or less regardless of the symptoms, the blood pressure gradually rises and may increase from 15 to 30 mm. of mercury. The pulse rate and respirations change little during this stage, which occupies from one-half to several hours. The value for blood sugar varies between wide limits, but as the attack progresses, there is a tendency for it to diminish gradually. Rarely is the hypoglycemic attack initiated by a convulsion or by stupor, though occasionally the history as given by the patient or his family may suggest the absence of any prodromal period.

12. Unverricht: Spontanhypoglykämie als transitorisches Symptom, Deutsche med. Wchnschr. **61**:207-209 (Feb. 8) 1935.

The third stage is that of stupor or coma. Invariably, if the attack progresses, the patient passes into a state of deep stupor or coma, which may persist from a minute to hours, or even days. During this stage there may be marked perspiration and salivation. Convulsive phenomena of variable types appear, and other neurologic signs develop in the form of changes in reflexes, nystagmoid movements of the eyes, motor palsy or disorders in movement. The blood pressure usually continues to rise during this stage, regardless of the coma; the pulse rate may increase, and the respirations may vary, depending on the motor activity; the temperature drops and at times may be several degrees below normal.

The fourth stage is that of recovery. With recovery from the deep hypoglycemic state, which may be spontaneous or the result of administration of food (dextrose) or epinephrine, the patient rapidly regains his state of "well-being." The rapidity of recovery is frequently incredible. The patient may appear to be snatched from the very doors of death and in ten or fifteen minutes may be entirely normal. Occasionally, a period of dulness and apathy supervenes, which may persist for several hours, or even days. Rarely, there are other residual signs of a neurologic character, indicating that an injury, such as motor palsy, persisting pathologic reflexes or aphasia, has been sustained by the nervous system. These disturbances are usually transitory, and in the course of from a few hours to a few days they tend to disappear.

As has been pointed out by Wilder,[13] John [14] and others, the depth of the coma and the severity of the symptoms need have no relation to the amount of insulin that has been administered or to the level of the blood sugar during the period of hypoglycemia. These are observations that are frequently made in the insulin shock treatment of patients with schizophrenia.

It is not within the scope of this paper to discuss the etiology of hypoglycemia or the mechanism by which it disturbs the normal functioning of the nervous system. As pointed out by Mann and Magath,[15] hypoglycemia may occur in hepatectomized dogs, and it is known that disease of the pancreas need not be the only factor in the production of hypoglycemic symptoms. It appears reasonable to assume that the neurologic phenomena are the result of a physicochemical change in the nervous system that is bound up in some manner with carbohydrate

13. Wilder, R. M.: Hyperinsulinism (Colver Lecture), Internat. Clin. **2**:1-18 (June) 1933.

14. John, H. J.: The Lack of Uniformity in the Insulin Reaction, Am. J. M. Sc. **172**:96-106 (July) 1926.

15. Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver: II. The Effect of the Removal of the Liver on the Blood Sugar Level, Arch. Int. Med. **30**:73-84 (July) 1922; III. The Effect of Administration of Glucose in the Condition Following Total Extirpation of the Liver, ibid. **30**:171-181 (Aug.) 1922.

metabolism. Whether these neurologic symptoms are due to a change in oxygen tension, nitrogen metabolism, carbon dioxide content of the blood or the like remains a problem for added study. Needless to say, the added knowledge that is being gained regarding cerebral physiology by the careful study of patients treated with insulin shock should, at least for the time being, justify the use of this method. The classification in table 1, which is based largely on cases we have observed personally, illustrates the complexity of the problem.

The diagnosis of hypoglycemia is usually easy if the condition is kept in mind. As has been pointed out by Allan,[8] Kepler and one of us (F. P. M.) [16] and others, one cannot make a positive diagnosis from the symptoms of hypoglycemia alone. The fasting value for blood sugar must be known. Only too often, patients with hypoglycemia are not able to give an accurate account of their symptoms, as they usually have no memory of the attack and rely on hearsay for their statements.

TABLE 1.—*Etiologic Classification of Hypoglycemic States*

1.	**Induced hypoglycemia; in insulin therapy**
2.	**True hyperinsulinism; due to tumors or hyperplasia of islands of Langerhans**
3.	**Spontaneous hypoglycemia (of unknown origin)**
4.	**Hepatogenous hypoglycemia; may occur in presence of damage to the liver**
5.	**Hypoglycemia from adrenal or pituitary insufficiency**
6.	**Physiologic hypoglycemia**

There is also a tendency for the symptoms to develop under such unusual circumstances and at such peculiar times that the nature of the condition is readily overlooked.

To establish the diagnosis of hypoglycemia one should determine: (1) that the attacks can be precipitated by abstinence from food, (2) that they are associated with subnormal values for blood sugar and (3) that the injection of dextrose will relieve the symptoms. It is always advisable in the presence of such symptoms as syncope, unconscious attacks, mental lapses, hysterical seizures or bizarre symptoms of any type that are not readily explained on the basis of known neurologic or psychiatric disturbances to insist on a determination of the fasting value for the blood sugar.

The diagnoses that are made most frequently in cases of hypoglycemia prior to recognition of the true nature of the condition cover, as has been said, the entire range of neurologic and psychiatric conditions. In table 2 is a list of some of the more common conditions with which hypoglycemia is confused. We have grouped the items together under general headings, since usually descriptive terms are employed in describing the hypoglycemic state. It must be kept in mind that hypo-

16. Kepler, E. J., and Moersch, F. P.: Psychiatric Manifestations of Hypoglycemia, Am. J. Psychiat. **94**:89 (July) 1937.

glycemic states are frequently overlooked and for a long period may masquerade under the guise of a functional disorder. The converse is also true, as has been noted by Jordan,[17] Whipple and Frantz,[18] Jones,[19] Vonderahe[20] and others, namely, that at times a diagnosis of hypoglycemia (physiologic hypoglycemia) is made on inadequate grounds because of suggestive symptoms of hypoglycemia, when in reality the patient is suffering from an anxiety neurosis, a functional gastro-intestinal disorder or idiopathic epilepsy.

After observing these profound hypoglycemic attacks, one wonders how patients can withstand the effects of these severe reactions without ill effect on the nervous system. A review of the literature soon establishes the fact that hypoglycemic states are not without danger in this respect. Bowen in 1933 collected twenty cases of fatal hypoglycemia

TABLE 2.—*Incorrect Diagnoses Frequently Made in Cases of Hypoglycemia (Differential Diagnosis)*

Psychoneurosis: Hysterical attacks, apathy, weakness, "nervousness"
Epilepsy: Petit mal, grand mal, convulsions, unconscious attacks
Confusional states: Somnambulism, fugues, amnesic attacks
Alcoholism: "Drunken behavior"
Vertigo: Attacks of dizziness, syncope
Tumor of the brain
Encephalitis: Lethargy, disturbance in behavior, narcolepsy
Acute delirium: Manic attacks
Cerebrovascular lesions
Dementia paralytica
Hyperthyroidism
Coma or stupor

and stated that up to that year Joslin[21] had reported four deaths from insulin hypoglycemia. Several deaths have been reported since the introduction of Sakel's insulin shock treatment for schizophrenia, and practically every writer on the subject of insulin therapy warns against the possibility of a fatal outcome. In our own experience we have had no permanent ill effects from insulin therapy in cases of schizophrenia. In cases of hypoglycemia other than that of the insulin-induced type, we have observed various transitory palsies, aphasia, paresthesias, mental dulness and so forth. That hypoglycemia of endogenous character may be a serious affliction is attested by the fact that surgical intervention offers the only permanent relief in cases of hyperinsulinism. Thus far

17. Jordan, W. R.: Neurological Manifestations of Hypoglycemia, New England J. Med. **209**:715-719 (Oct. 12) 1933.

18. Whipple, A. O., and Frantz, Virginia K.: Adenoma of Islet Cells with Hyperinsulinism: A Review, Ann. Surg. **101**:1299-1335 (June) 1935.

19. Jones, M. S.: Hypoglycaemia in the Neuroses, Brit. M. J. **2**:945-946 (Nov. 16) 1935.

20. Vonderahe, A. R.: Personality Change in Hypoglycemia, J. Med. **17**:189-190 (June) 1936.

21. Joslin, E. P., cited by Bowen and Beck.[4]

there is no adequate treatment for the large group of patients with so-called spontaneous or idiopathic hypoglycemia.

Up to the present, there has been no unanimity of opinion regarding the existence of pathologic changes in the central nervous system resulting from hypoglycemia. Experimental studies on animals have not been convincing. Wohlwill,[22] Grayzel[23] and Stief and Tokay[24] reported rather characteristic cellular changes, whereas the experience of other investigators, who used rabbits, coincided more with that of Baker and Lufkin[25] and indicated that there is no characteristic pathologic picture. In most cases of hypoglycemia in which careful histologic studies were carried out, petechial hemorrhages were reported to have been observed throughout the central nervous system, such as those in the cases described by Baker and Lufkin,[25] Terbrüggen[26] and Bowen and Beck.[4] Others, like Bodechtel[27] and Wohlwill, have reported extensive zones of degeneration in the cortex of the brain, such as were seen by Gildea and Cobb[28] as the result of anemia, by Courville[29] in patients who had died of nitrogen monoxide anesthesia or by Spielmeyer[30] as the result of carbon monoxide poisoning. The changes in the nerve cells were nonspecific. Terplan[31] expressed the same opinion after studying three cases in which the patients died as the result of insulin shock. The last-named author noted changes similar to those observed by Wohlwill, which also resembled those seen in our two cases. From these pathologic studies it is apparent that hypoglycemic states are in the nature of profound reactions and that fatalities may occur both in spontaneous and in induced types of hypoglycemia.

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22. Wohlwill, Friedrich: Ueber Hirnbefunde bei Insulin-Ueberdosierung, Klin. Wchnschr. **7**:344-346 (Feb. 19) 1928.

23. Grayzel, D. M.: Changes in Central Nervous System Resulting from Convulsions Due to Hyperinsulinism, Arch. Int. Med. **54**:694-701 (Nov.) 1934.

24. Stief, A., and Tokay, L.: Beiträge zur Histopathologie der experimentellen Insulinvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:434-461, 1932.

25. Baker, A. B., and Lufkin, N. H.: Cerebral Lesions in Hypoglycemia, Arch. Path. **23**:190-201 (Feb.) 1937.

26. Terbrüggen, August: Anatomische Befunde bei spontaner Hypoglykämie infolge multipler Pankreasinseladenome, Beitr. z. path. Anat. u. z. allg. Path. **88**:37-59 (Nov. 19) 1931.

27. Bodechtel, G.: Der hypoglykämische Shock und seine Wirkung auf das Zentralnervensystem, zugleich ein Beitrag zu seiner Pathogenese, Deutsches Arch. f. klin. Med. **175**:188-201 (May 12) 1933.

28. Gildea, E. F., and Cobb, Stanley: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876-903 (May) 1930.

29. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129-245 (May) 1936.

30. Spielmeyer, Walther: The Anatomic Substratum of the Convulsive State, Arch. Neurol. & Psychiat. **23**:869-875 (May) 1930.

31. Terplan, K.: Changes in the Brain in a Case of Fatal Insulin Shock, Arch. Path. **14**:131-132 (July) 1932.

In the cases in which patients have died of hypoglycemia neuropathologic studies have been relatively few, and it is for this reason that we are reporting our two cases in some detail.

REPORT OF CASES

CASE 1.—A farmer aged 35 was brought to the hospital on March 29, 1936, because of attacks of confusion, stupor and convulsions. On admission he was in a state of stupor, and the history had to be obtained from his wife.

He had been in good health up to a year before, when he had had a momentary attack of loss of consciousness. He had experienced no further trouble until early in November 1935, when his wife observed that as he came in to dinner one day, he sat down at an unaccustomed place at the table and passed the food in a peculiar way, as if he were in a daze. He complained of feeling dizzy and perspired profusely. Within four or five minutes he appeared well. In the following three weeks he had three similar attacks of loss of consciousness.

On November 26 the patient complained of a severe headache, refused his supper and went to bed. The following morning he was in a deep stupor and could not be aroused. He was taken to a hospital and continued in this stuporous condition for about six days. On arousal from the stupor his right arm and leg were weak, and while this cleared up rapidly, it was thought that his right hand never fully recovered its strength. When he left the hospital, four weeks after his admission, he was feeling well. His wife was told that it was believed at first that he had a tumor of the brain but that in view of his recovery he must have had a cerebral hemorrhage. He remained well for a month, when he again had an attack of unconsciousness, which lasted about an hour. In the week prior to his admission to the clinic he complained of a dull frontal headache. On March 28 he fell asleep and could not be aroused, and at 3 o'clock the next morning he had a generalized convulsion. He remained in a dazed, semistuporous condition all day and had another convulsion of short duration while being transported to the clinic.

On admission, emergency studies revealed no apparent cause for the stupor. There was no sugar in the urine. Examination of the ocular fundi showed no evidence of choked disks. The patient was given 500 cc. of 20 per cent solution of dextrose intravenously, and about five minutes later he awakened, talked clearly and answered questions coherently. On the following morning he was in stupor again, but he did not arouse after an intravenous injection of 300 cc. of a 25 per cent solution of dextrose. General physical examination revealed little of importance. Roentgenologic examination of the thorax and head revealed nothing abnormal. Neurologic examination was unsatisfactory because of the patient's lack of cooperation. As far as could be determined, the cranial nerves were normal. All the deep reflexes were sluggish; the abdominal reflexes were absent, and the plantar responses were of an extensor type. Motor and sensory examinations were impossible.

The patient's condition changed little in the next few days. At times the stupor appeared to clear up, but within a short time he was again in deep coma. In view of the history, we were of the opinion that we were dealing with a deep-seated neoplasm, probably in the third ventricle. Consequently, on April 1 a ventriculographic study was carried out, which showed slight dilatation of the lateral ventricles and the third ventricle but no evidence of a focal cerebral lesion. Examination of the cerebrospinal fluid obtained at the time of the ventriculographic study showed nothing abnormal. The patient continued to be in a deep

stupor, his temperature gradually mounting to 103 F. He had to be fed by tube, and fluids, consisting of a 5 per cent solution of dextrose and a 1 per cent solution of sodium chloride, were administered daily by intravenous injection. Examinations of the urine for lead and arsenic gave negative results. It was noted that at times the patient was rigid and that any stimulation precipitated generalized jerking movements of the extremities. At times also the right arm appeared to be weak, but this could never be verified. On April 8 the patient appeared to arouse slightly; after this, however, the stupor deepened; the temperature mounted to 104 F., and signs of pneumonia developed. The patient died on April 15, fifteen days after the ventricular study. The antemortem diagnosis was unlocalized tumor of the brain, probably deep seated in the region of the third ventricle or aqueduct of Sylvius, or encephalitis.

Observations at Necropsy.—The immediate cause of death was bilateral bronchopneumonia, with abscesses in the lower lobes of both lungs, which on microscopic examination proved to be of the inhalation type, as foreign material was present in the smaller bronchi and abscesses. In the tail of the pancreas was a circumscribed but nonencapsulated tumor, which measured 7.6 by 5 by 5 cm. This tumor was reddish brown and had three small calcified nodules near its center. No gross lesions were observed in the other organs of the thorax and abdomen. Histologic examination of the neoplasm in the tail of the pancreas revealed it to be a typical adenocarcinoma (grade 1) arising from the islands of Langerhans. It was similar to the one described by Wilder, Allan, Power and Robertson [32] except that it was less malignant.

On study of the entire central nervous system no gross lesion was noted. The brain had a slightly edematous appearance. The spinal cord appeared normal. Sections were taken from the various lobes and the basal nuclei, pons, cerebellum, medulla and spinal cord, and all were stained with hematoxylin and eosin and cresyl violet and by the modified silver nitrate impregnation method for nerve cells, axis-cylinders and so forth. These sections showed edema of the brain tissue, extensive nerve cell degeneration and glia cell changes. Several sections from the frontal lobes showed approximately the same changes. The meninges and meningeal blood vessels were normal. In the cortex there was no inflammation or perivascular collections of cells, and the blood vessels were normal. There was well marked edema with distention of the perivascular spaces, clear spaces around all the nerve cells and acute swelling of the oligodendroglia cells. Around the swollen and degenerated nerve cells were collections of oligodendroglia cells, which varied from two to eight; there were also astrocytes and sometimes a rod cell (microglia cell). This collection of glia cells around the nerve cells is generally referred to as "satellitosis," and it was well illustrated in this instance.

Practically none of the nerve cells in the cerebral cortex were normal, and they were not arranged in an orderly manner, as in normal brain tissue. The apical dendrons as a rule pointed not toward the pia mater but in all directions. The dendrites were either swollen and fragmented or could not be seen at all; sometimes they assumed a "corkscrew" appearance. Practically no cells had the typical appearance of pyramidal cells but were swollen and globular; that is, they were undergoing chromatolysis, so that no Nissl granules or chromatin material was visible. Frequently, only the faintest shadow of pyramidal cells (ghost cells) could be seen. The nuclei were usually swollen and eccentric, and the nucleolus

32. Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas-Hyperinsulinism and Hypoglycemia, J. A. M. A. **89**:348-355 (July 30) 1927.

was also larger than normal. In some places the ganglion cells had completely disappeared, and only the collections of satellite cells were left. In the remaining nerve cells the intracellular neurofibrils had disappeared or were swollen, clumped or fragmented. Only occasionally were we able to observe vacuolated cells, and still more rarely did we see the so-called spiky cells. All layers of the cortex were involved, but those containing the largest cells seemed to be most extensively involved, probably because they were the most obvious.

In the cortex, particularly in the posterior convolutions of the frontal lobes and in the parietal lobes, there were small islands in which there was an increase in the number of glia cells. These islands closely resembled the glial proliferations seen commonly in the cortex in cases in which patients have died of dementia

Fig. 1 (case 1).—Photomicrograph (modified silver impregnation method; × 400) showing degeneration of axis-cylinders, with swelling, beading and fragmentation.

paralytica. In these islands the nerve cells were more degenerated than in most other portions of the cortex. These islands were not limited to any one cell layer of the cortex, but were more common in the third layer. All the smaller blood vessels were dilated and full of erythrocytes. The white matter underneath these islands showed early degeneration of the myelin and definite degeneration of the axis-cylinders, such as swelling, vacuolation, beading, and fragmentation (fig. 1), as well as proliferation and degeneration of the astrocytes and acute swelling of the oligodendroglia cells. There was no apparent increase in the number of microglia cells. In the remaining portions of the white matter most of the astrocytes had swollen cell bodies with few visible processes. Occasionally two of these had become fused, forming a gemästete glia cell. The axis-cylinders appeared normal, as did the myelin sheaths.

Changes in the parietal, occipital and temporal lobes were similar to those in the frontal lobes. In the left occipital lobe and in the right hippocampus there

were small "areas of devastation." All the nerve cells in these two areas had completely disappeared; the astrocytes had proliferated, and there were numerous rod cells and some scavenger cells containing fat droplets. These foci were sharply circumscribed. The area in the occipital lobe involved the lower portion of the visual cortex, while that in the hippocampus had destroyed a portion of the fascia dentata. In these areas there was marked proliferation of the smaller blood vessels, but no occluded blood vessels could be seen. The changes in all other portions of the cerebral cortex were similar to those observed in the frontal lobes.

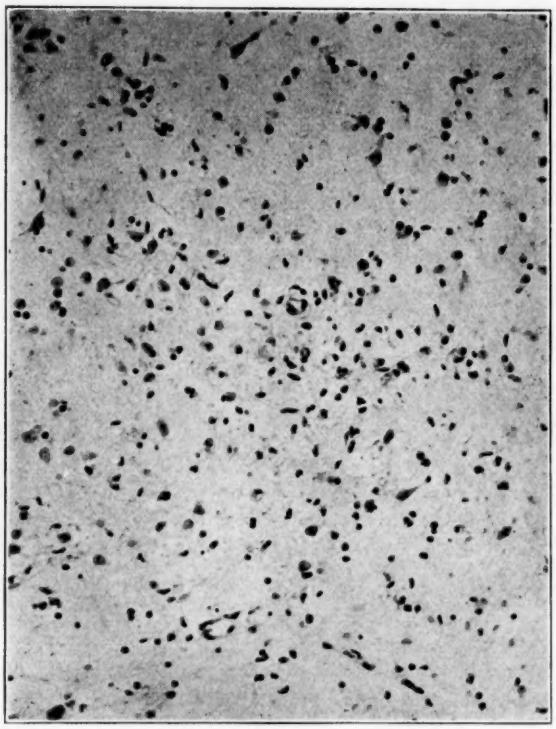

Fig. 2 (case 1).—Photomicrograph (hematoxylin and eosin; × 160) showing a focus of glia cell proliferation with disappearance of nerve cells.

The histologic changes in the basal nuclei, substantia nigra and midbrain were similar to those in the cerebral cortex, namely, edema, swollen and proliferated glia cells and profound changes in the nerve cells. The cerebellum was better preserved than the cerebrum; in fact, it was almost normal. The changes in the medulla oblongata varied greatly; some small areas were normal, and in other small areas (fig. 2) complete degeneration of the nerve cells and excessive proliferation of the glia cells were outstanding. Sections taken from various levels of the spinal cord showed it to be normal except in a small portion of the mid-lumbar enlargement. In these sections about two thirds of the nerve cells of one

anterior horn had been destroyed, and these cells had been replaced by proliferation of the glia, especially the astrocytes (fig. 3).

The dorsal root ganglia were normal, and we were unable to demonstrate any abnormal changes in the peripheral nerves.

CASE 2.—A man aged 47 was first examined on October 9, 1928. In 1924 he had noted occasional transitory "dizzy spells" or periods of confusion, which came on about 3 or 4 p. m. He knew what he wanted to do but lacked the power to make his "mind work." He discovered accidentally that eating a sandwich or

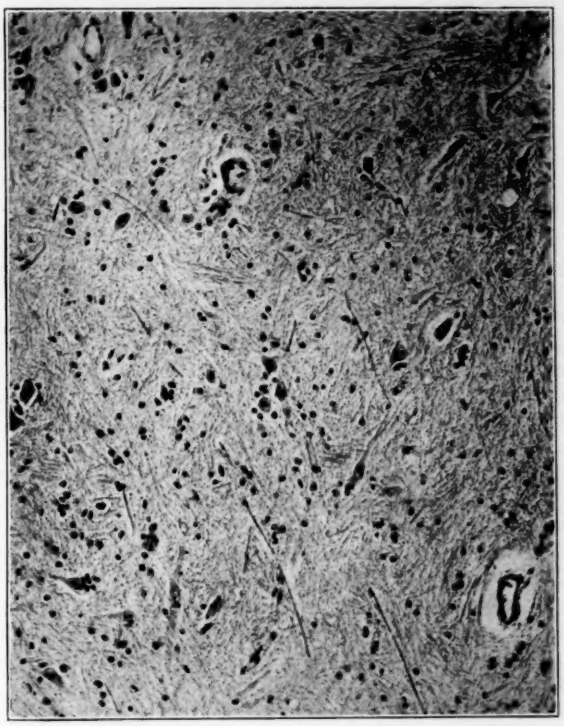

Fig. 3 (case 1).—Photomicrograph (hematoxylin and eosin; × 125) showing degeneration and disappearance of the nerve cells of the anterior horn in the lumbar region of the spinal cord, with proliferation of the glia cells.

drinking a cup of coffee would quickly relieve him of his apathy, and he made it a practice to have an afternoon lunch, the omission of which was likely to have disastrous consequences. He also observed that these attacks were more likely to occur on days when he worked hard.

In 1925 somnambulistic tendencies developed: The patient, for example, would wander out of his apartment and find himself in some strange place. On one occasion he found himself in his car on his way to work, and he had no recollection of having dressed or taken his car out of the garage. In September 1926 he awoke one morning to find himself in a hospital strapped to the bed in a straitjacket; he was told that he had become delirious and destructive during the night. After this he had frequently awakened in the morning to find his room disarranged,

without any knowledge of having been disturbed. On his own initiative he had tried to have two feedings during the night. If he failed to hear the alarm clock, he invariably had an attack of sleep-walking, confusion or delirium. On this regimen of frequent feedings he put on much weight.

His local physician, suspecting the true nature of the patient's trouble, advised him to enter a hospital, which he did in August 1928. He was there for sixteen days, but all that was accomplished was his being ordered to the psychiatric ward because of his nightly tantrums, which were looked on as psychogenic. The patient left this hospital with the written information that he had a "nervous condition." His physician, however, appreciating the true nature of the ailment, referred him to the clinic with the diagnosis of hypoglycemia, though he himself had never witnessed an attack or made a determination of the fasting value for blood sugar.

Examination of the patient on admission (October 9, 1928) revealed that he was 25 pounds (11.3 Kg.) overweight. He was able to relate the history in a coherent manner, and both general and neuropsychiatric examinations showed little of importance. During his stay in the hospital he was observed in numerous attacks, of varying severity. If his usual program of feeding was interfered with, signs of hypoglycemic shock invariably developed. The sequence of events was more or less as follows: He first became apathetic; there were slowing of all mental processes and lack of ability to concentrate; profuse perspiration appeared, breathing became slower and deeper; the gait was staggering, and there might be diplopia. He was like one who was mildly intoxicated. If the attack was permitted to go further, he became more confused, irritable and quarrelsome; he refused food and appeared to fear eating. He might become very active and destructive and require restraint, or he might pass into deep coma. As a rule an attack lasted about an hour, when he would make a spontaneous recovery. The attack could be stopped at any stage by the intravenous injection of dextrose. The fasting values for blood sugar ranged from 37 to 56 mg. per hundred cubic centimeters. On January 2, 1929, exploration of the pancreas was undertaken, but masses were demonstrable. From a third to a half of the pancreas was resected. Microscopic examination proved it to be normal pancreatic tissue.

The patient returned to the clinic in May 1929. He had made an excellent recovery from the operation, but the hypoglycemic symptoms remained unchanged. Owing to the difficulty of carrying out his feeding program, which extended throughout the twenty-four hours, he had repeatedly been hospitalized by his local physician. At home he had been unable to keep to his regimen, and it had often been necessary to call "a gun squad to hold the patient while in an attack." He was finally admitted to a hospital on August 17, 1932, where he remained until his death. It is interesting to note that on the morning of December 26, 1934, he had a severe hypoglycemic reaction. He was unable to swallow and was given epinephrine and opiates; as soon as he was quiet enough for a needle to be placed in his vein, he was given 100 cc. of a 10 per cent solution of dextrose. He became quiet and passed into a deep stupor, from which he failed to arouse. He died at 3 p. m. the same day.

Postmortem examination was performed elsewhere, the pathologic diagnosis being hypoglycemia due to hyperinsulinism and bronchopneumonia. Small portions of the brain were received for study. This tissue, however, had been fixed in a 10 per cent concentration of a commercial solution of formaldehyde for about one and a half years, and the staining methods that could therefore be used were limited. In the pons there were marked edema, characterized by dilatation of the perivascular spaces, widening of the spaces around the nerve cells

and acute swelling of the oligodendroglia cells. The myelin sheaths were separated from each other, giving the appearance of a delicate mesh. Many of the other changes observed in this tissue were of similar nature, and some were of definite antemortem origin. There were some astrocytes, which were swollen and showed beginning degeneration, and in portions of the tissue the changes in the astrocytes approached the formation of gemästete glia cells. Some of the nerve cells had undergone acute degenerative changes, but the nuclei for the most part remained near the center of the cells. A few cells had undergone almost complete disintegration. The dendrites of many cells had a corkscrew appearance; some were fragmented, while others contained vacuoles. In the same cells the cytoplasm was swollen and vacuolated. There was a large number of cells which stained dark diffusely; in these the nucleus could not be distinguished, or the cells had undergone "pyknosis."

The blood vessels, particularly the arterioles, venules and capillaries were extremely dilated and "stuffed" with erythrocytes. There were no large hemorrhages, although several extravasations of erythrocytes into the dilated perivascular spaces had occurred.

Several portions of the cerebral cortex were also received for study, and in some instances we were unable to identify the region of the brain from which they were removed. However, they all showed changes similar to those which we noted in the pons, but for the most part degeneration was not profound. The most interesting change was noted in some of the cells which had undergone chromatolysis. In many places two or more of these swollen cells had become fused, forming a "pseudogiant" cell in which the nuclei of the original nerve cells were retained but the nucleoli were swollen and indistinct. There was little difference in the acute cellular changes in the various layers of the cortex, although the third and fifth layers seemed to be most profoundly affected. In some places the cells were so swollen that they resembled "globules," and many bizarre shapes were present. The changes present in the cortex varied in degree and intensity much more than those in the pons. There were no areas in which we were able to demonstrate previous insults to the cells, such as so-called fallen-out areas from which masses of nerve cells had disappeared. With the silver impregnation method we observed changes in the intracellular neurofibrils; these had become clumped, swollen, fused and fragmented and in some instances had disappeared.

COMMENT

Many of the changes that we noted in these cases can be observed in the nervous system in cases of several other diseases in which the patients have died in coma. There were alterations in the nerve cells which were unusual, namely, the fusion of several nerve cells to form pseudogiant cells. The vacuolation of some nerve cells and the pyknotic changes in others we believe are the result not simply of coma but of definite, though not specific, degeneration which occurred ante mortem. The chromatolysis or acute swelling, as well as the pyknosis or ischemic changes in the nerve cells (Spielmeyer), is generally accepted as existing from twenty-four to forty-eight hours before death. One phenomenon, however, is always accepted as ante mortem, namely, the swelling and degeneration of the astrocytes and the formation of gemästete glia cells.

SUMMARY

In summary, it may be stated that while hypoglycemic states are relatively uncommon, the physician must be "hypoglycemia conscious" to recognize them, because the symptoms are so bizarre. Neurologic symptoms are invariably a part of the hypoglycemic attack, and they may be exceedingly variable and present themselves under the guise of divers disorders. It has been recognized that severe and frequently repeated attacks of hypoglycemia are not without danger, from the standpoint both of transitory changes in the central nervous system and of the possibility of a fatal termination. It is important to appreciate the possibility of these dangers since, with the promiscuous use of insulin shock therapy for schizophrenia, one may expect to encounter some unfavorable reactions, if not an occasional fatality.

There is no unanimity of opinion regarding the pathologic changes that take place in the central nervous system after death from hypoglycemia, either in animals or in man. The pathologic alterations observed in our two cases, while fairly definite, are not easy of interpretation. Hypoglycemia produces either multiple petechial hemorrhages in the brain (which is the most common change) or degeneration of some of the cells. We observed some petechial hemorrhages in the pons in case 2, but the outstanding change in both case 1 and case 2 was degeneration of some of the nerve cells. This degeneration varied from place to place, and we are certain that most of it was ante mortem, especially the changes in the axis-cylinders and in the areas in which complete disintegration of the nerve cells had occurred. Changes in the astrocytes are usually accepted as occurring before death. We also think that many of the nerve cells which showed early acute degeneration could have been restored to normalcy and have assumed their normal function under favorable circumstances. This would support the idea that in cases in which patients are suffering from so-called insulin shock the nerve cells have undergone early acute degeneration but not irreparable degeneration. However, the margin between irreparable and reparable degenerative changes must at times be very narrow. The changes which we have observed in the nerve cells may account for most of the neurologic signs presented by the patients as the result of a hypoglycemic attack.

ABSTRACT OF DISCUSSION

DR. FRANK N. ALLAN, Boston: The attitude of the medical profession toward hypoglycemia has gone through a cycle since the discovery of insulin. At first insulin reactions were regarded with apprehension. Many patients suffering from diabetes were allowed to go untreated or undertreated because of fear of the consequences of overtreatment. Later on reactions occurred in so many patients with no apparent harm that they came to be regarded with indifference.

In recent years, however, more attention has been paid to the danger, particularly with regard to the heart, and now the changes demonstrated in the nervous system show further reason for caution.

Employment of insulin by diabetic patients is usually a simple matter, but medical supervision is essential. This is even more true in regard to the new, slowly acting insulin, since reactions may occur at unexpected times. It should be emphasized, however, that even in cases of diabetes complicated by serious heart disease, insulin can be used with safety if careful attention is given to adjustment of the diet and the insulin dosage.

Hypoglycemia occurring in patients treated with insulin can usually be recognized easily, and treatment with sugar can be given to avert accident. Spontaneous hypoglycemia may be much more serious. It can be recognized only by familiarity with the various psychiatric and neurologic manifestations presented by Dr. Moersch and Dr. Kernohan. Early diagnosis and protection against prolonged hypoglycemia are vitally important to prevent not only temporary incapacity but damage to the central nervous system, which may cause permanent disability, or even death.

RESULTS OF TREATMENT OF ATHETOSIS BY SECTION OF EXTRAPYRAMIDAL TRACTS IN THE SPINAL CORD

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CLASSIFICATION OF THE DYSKINESIAS

Certain disorders characterized by abnormal involuntary muscular movements have been grouped together as "diseases of the extrapyramidal system," chiefly on the basis of the localization of the lesions observed at autopsy (Wilson,[1] Herz [2]). They include athetosis, dystonia, torsion spasm, spasmodic torticollis, ballism, chorea, myoclonus and paralysis agitans. An important reason for excluding paralysis agitans from this list has already been given in a previous paper,[3] namely, that an extensive section of extrapyramidal motor pathways makes the tremor rigidity neither better nor worse. Further, recent pathologic investigations [4] have appeared to indicate that the alterations are by no means confined to the basal nuclei. No cases of chorea of either the Sydenham or the Huntington type have been sufficiently studied by modern physiologic methods to permit a comparison with the other diseases in the group. But the remaining syndromes in the list possess so many manifestations in common that they may provisionally be grouped together. These manifestations are as follows:

1. The character of the abnormal movement is similar in all. It is slower than the most rapid voluntary movements; it affects sometimes one, sometimes another, group of muscles, and the contraction is maintained or altered slowly once it occurs and gives rise to gross, usually varied, movements of the extremities and trunk.

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Read before the Section on Nervous and Mental Diseases of the American Medical Association, Atlantic City, N. J., June 9, 1937.

1. Wilson, S. A. K.: Disorders of Motility and of Muscle Tone, with Special Reference to the Corpus Striatum: IV. Athetosis, Lancet **2**:216 (Aug. 1) 1925.

2. Herz, E.: Die amyostatischen Unruheerscheinungen: Klinisch-kinematographische Analyse ihrer Kennzeichen und Begleiterscheinungen, J. f. Psychol. u. Neurol. **43**:3, 1931.

3. Putnam, T. J.: Treatment of Athetosis and Dystonia by Section of Extrapyramidal Motor Tracts, Arch. Neurol. & Psychiat. **29**:504 (March) 1933.

4. Benda, Paul: Personal communication to the author.

2. The various types of movement may be combined in a single case. Thus, involuntary grimacing, lack of control of the tongue, typical torticollis, athetosis of the fingers, ballism of the arms and dystonia and torsion of the trunk were all observed to coexist in five cases in the series.

3. Electromyographic records show irregular waves of impulses, entirely different from the slower regular rhythm of paralysis agitans.[5] Further report on this subject is in preparation.

4. Encephalograms usually show dilatation of the ventricles at the expense of the basal nuclei, and only rarely and irregularly any cortical defect.[6] Similar distortions may, however, be found in diseases of the paralysis agitans and chorea groups.[7] This is perhaps to be expected, since there may be similarities in the gross appearance of the brain post mortem in cases of all these types.

5. The movements persist with large doses of scopolamine and the barbiturates.

6. Section of the anterior columns of the spinal cord mitigates the symptoms on the same side below the level of operation.[8]

For the purpose of this paper, therefore, I propose to refer to the conditions which in general meet the criteria just enumerated as "athetosis." It will be seen that the cases reported here form a fairly homogeneous group. Whether all cases of torticollis without involvement of the face, trunk or extremities should be included may be a debatable point. It is my belief that while in some cases the disease is psychogenic,[8] in others it is caused by impulses coming over the extrapyramidal pathways as a result of organic lesions[9] and is benefited by surgical treatment.[10] At any rate, as will be seen, the condition cannot be treated by section of the extrapyramidal pathways for technical reasons and the subject will not be considered further here.

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5. Lindsley, D. P.: Electromyographic Studies of Neuromuscular Disorders, Arch. Neurol. & Psychiat. **36**:128 (July) 1936.

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MATERIAL

This report is based on twenty-seven cases in which section of one or both anterior columns, with or without destruction of the anterior roots, was carried out. In twenty-three cases the condition met most of the criteria already laid down and is therefore referred to as "athetoid." The series includes three cases of postoperative death, but in two death occurred after an interval long enough to show that the abnormal movements were profoundly modified by the operation. In the four additional cases operation produced no result. Five cases of the whole group have been reported before.[3]

The ages of the patients suffering from athetosis varied from 8 to 56 years. There were twelve female and eleven male patients. In nine cases the athetosis was confined to one side (usually predominating in the arm), and in thirteen it was bilateral, though usually more pronounced on one side than on the other. In nine of the cases of bilateral athetosis the neck and face were also involved. In two cases only one leg was seriously disabled by generalized athetosis, which was mild in the other extremities. Cases occur in which both arms, but not the neck, trunk or legs, are the seat of violent involuntary movements. I have seen two such instances, but since operation has not been performed, they are not included in the series.

There was a history of difficult delivery, asphyxia or definite trauma at birth in fifteen cases, in ten of which the disease was bilateral. Some weakness, incoordination or involuntary movements were observed either immediately or after intervals up to two and a half years. In six cases slow, irregular progression of the movements occurred, even as late as the twenty-eighth year.

In two cases already reported,[3] the disease occurred in sisters and was rather rapidly progressive. In another, included in the same paper, it appeared to be the result of a vascular accident occurring during the course of acute pneumonia. In two cases the symptoms followed several years after an injury to the head. No cause was known in four cases, in all of which the disease was progressive.

Patients suffering from athetosis are often judged to be feebleminded, on account of their uncouth appearance and behavior. This is especially the case if the face and tongue are involved. How unjust such a suspicion may be is shown by the fact that twelve of the patients in the present series can definitely be stated to possess normal or superior mentality, on the basis of psychometric tests or of performance in school or elsewhere. Only three patients were definitely subnormal; in the case of the rest information is incomplete. Of course, if the disease begins early in life and is severe, education may be greatly hampered. In four patients a tendency to paranoid thoughts was observed, and two of them passed through a mild, but definite, psychosis.

All the patients were practically disabled by their disease and lived secluded lives. In nine cases the difficulty was mainly in the use of one hand. Seven patients could scarcely walk; two were incapacitated by torticollis, and for four it was impossible to sit up or lie still in bed. The movements decreased when the subject was at ease and were exaggerated by any emotional strain in all instances. The movements usually ceased during sleep.

Ordinary neurologic examination was extremely difficult in all cases, due to the constant irregular movements. Some signs of injury to the pyramidal tract (Babinski's sign, hyperactive reflexes or clonus) were found in about half the cases.

METHODS OF TREATMENT OF ATHETOSIS

Comparatively little attention has been paid to treatment in cases of athetosis. The condition is often classified merely as "spasticity," though there is every evidence that it is entirely different in mechanism from the ordinary spastic paralysis resulting from injury to the pyramidal tract. Physical therapy and muscular reeducation have been recommended, especially by Carlson,[11] but I have not found anywhere in the literature a description of the principles which should guide it. The problem has little similarity with that presented by poliomyelitis or hemiplegia. Practically all the patients reported on here have had muscle training in competent hands before being referred for operation, sometimes with definite benefit. It is my impression that more is to be gained by psychotherapy—that is, by attention directed to sensitiveness and phobias—than by physical reeducation. Of course, the patients that respond well to training seldom come to a neurosurgeon, and this may be the explanation for the paucity of such cases in the present series. Retraining is a measure worth trying in every case.

The use of drugs has been of little avail. In many cases in this series bromides, barbiturates, members of the atropine series, harmine and bulbocapnine have been tried, without success. There are encouraging reports of the use of curare.[12]

Of surgical procedures, tenotomy and section of peripheral nerves are the operations in most general use. One or both of these procedures had been carried out in five cases of the severer form in the series. It is difficult to judge their value, but it appears that there may be a disadvantage in impairing the strength of an extremity when the difficulty is really one of coordination.

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11. Carlson, E. R.: Neurological Aspects and Treatment of Birth Injuries, New York State J. Med. **34**:831 (Oct. 1) 1934.

12. Burman, M. S.: Personal communication to the author.

The treatment of athetosis by operation on the central nervous system was apparently first attempted by Horsley [13] in 1909. In a case in which involuntary movements of one hand occurred, he excised the excitable motor cortex on the opposite side. The patient was relieved from the movements for a year but suffered severe loss of the finer control of the hand. Success in a similar operation has been reported by Sachs.[14] Bucy and Buchanan [15] and Bucy and Case [16] have reported two cases of athetosis in which they excised the premotor cortex (area 6 of Brodmann), with relief of abnormal movements. Other surgeons [17] have been less successful. I have known of some unrecorded failures and one death from this operation. It is probable that the proportion of good results could be raised by modern methods of study. The disability of the hand which necessarily results is a serious disadvantage, and an operation of this type for bilateral symptoms is practically out of the question. It is difficult to see how athetosis affecting the legs, trunk or neck could be attacked at the cortical level. The method, however, deserves further trial.

SECTION OF THE EXTRAPYRAMIDAL TRACTS

The operation used in the present series was first performed in 1931, as a result of considerations which are given in detail in a previous publication.[3] Briefly, the procedure is intended to sever the nonpyramidal motor pathways, which lie mainly in the anterior quadrant of the spinal cord. They have been subdivided into the vestibulospinal, the reticulospinal and the tectospinal pathways, but their respective fibers appear to intermingle to a great extent. There may be a few corticospinal fibers among them.[18] In the earlier operations a special attempt was made to sever the rubrospinal tract, but I have been unable to see that it made any difference in the results, and the necessary incision endangers the pyramidal tract.

The operation should be carried out as high in the cord as possible if the arms are involved. In most cases the second cervical interspace has been used. If two incisions are to be made, they should, of course,

13. Horsley, V.: The Function of the So-Called Motor Area of the Brain, Brit. M. J. **2**:125, 1909.

14. Sachs, Ernest: The Subpial Resection of the Cortex in the Treatment of Jacksonian Epilepsy (Horsley Operation) with Observations on Areas 4 and 6, Brain **58**:492, 1935.

15. Bucy, P. C., and Buchanan, P. N.: Athetosis, Brain **55**:479, 1932.

16. Bucy, P. C., and Case, T. J.: The Surgical Treatment of Unilateral Athetosis, Tr. Am. Neurol. A. **62**:112, 1936.

17. Foerster, O.: Zur Lehre der Erkrankungen des striären Systems, J. f. Psychol. u. Neurol. **25**:631, 1920; in discussion on Bucy and Case.[16]

18. Spiller, W. G., in discussion on Putnam.[3]

be spaced a segment apart. If the operation is on one side alone, the laminectomy should extend farther to that side than to the other, and the dura should be opened as far lateral as possible. For bilateral operation an oblique dural incision is often advantageous.

The cord may be rotated after severing a slip of the dentate ligament, without sacrificing posterior roots. Instead of using the guarded knife, as advised at first, I now make a longitudinal slit at the level of the anterior roots, insert a blunt hook and crush as much as possible of the anterior column against the anterior wall of the spinal canal. The certainty of producing sufficient destruction can be increased by

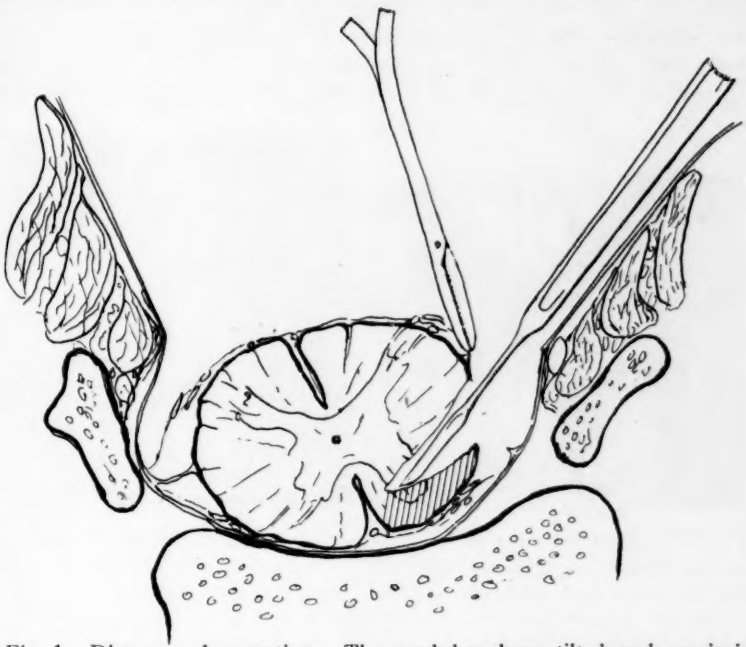

Fig. 1.—Diagram of operation. The cord has been tilted and an incision made at the level of the anterior roots, through which the anterior column is crushed or cut.

gentle strokes of a fine iridectomy knife within the opening thus made, avoiding injury to pial vessels (fig. 1). If bleeding occurs from the front of the cord, it can be controlled by placement of muscle pressure against the vertebral body by a blunt hook inserted in the incision in the cord and by hot irrigations.

If torticollis is an important symptom, this operation can be combined with section of the first three anterior roots. The fourth should be carefully preserved, as it contains so many fibers going to the phrenic nerve. Section of the spinal accessory nerve in the neck may also be extremely helpful. It is often wise to carry out the root sections first,

since the abnormal movements of the neck may otherwise persist with deep anesthesia and render the chordotomy difficult.

It is extremely dangerous to operate on both sides of the cord and the anterior roots at the same session. It was this attempt which led to two of the fatalities in the series, through interference with respiration and development of the "progressive confusional syndrome."[19] A respirator should be available in all instances, and transfusion should be given if the red cell count is reduced below 4,000,000.

Results of the Operation—Fatalities.—One fatality has already been reported in a previous paper.

Beverley, H., a girl of 11 years, suffering from rapidly progressive bilateral dystonia, had received some benefit from partial section of the anterior columns. In an attempt to increase the relief and to deal with torticollis, which had mean-

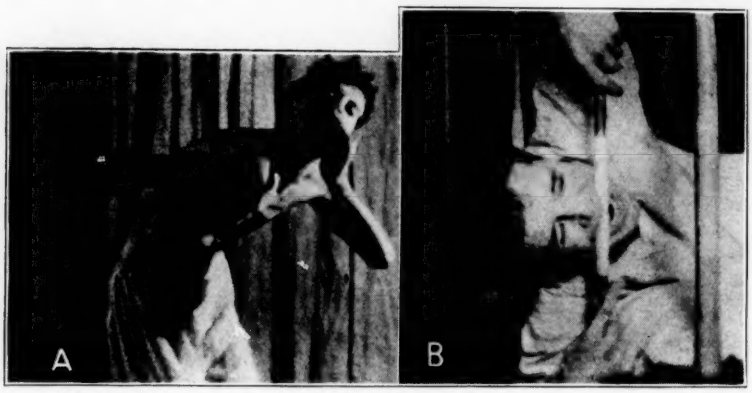

Fig. 2. (case 2).—Frederick K. *A*, dystonic attitude in walking, with protrusion of tongue. *B*, position habitually taken in bed, with the patient holding to the cross-bars with his teeth to inhibit torticollis and athetosis.

while developed, a more radical section was carried out, and the first three anterior roots were cut. The patient's respirations became poor, and she died within twelve hours.

The second case was that of Frederick K., a 25 year old law student, who was admitted on Feb. 26, 1933, complaining of difficulty in speech, involuntary protrusion of the tongue and turning of the head, which had come on gradually for two years. There had been a sudden exacerbation eight months before admission, since when there had been almost constant movements of neck and body except when he was asleep. There was no history of difficult delivery or of any precipitating factor.

The patient presented an amazing picture of dystonia affecting the face, neck and shoulders (fig. 2 *A*). The tongue and neck were in constant movement, and he walked with the head bent forward and one arm extended. The only position

19. Putnam, T. J., and Munro, D.: The Progressive Confusional Syndrome in Injuries of the Cervical Cord, in preparation.

in which he could lie still in bed was with his head between the bars, holding to one of them with his teeth (fig. 2 *B*). He spoke only by holding his tongue with his hand.

General neurologic examination revealed an otherwise essentially normal condition except for absence of the abdominal reflexes. The spinal fluid pressure was 140 mm.; there were a protein content of 50 mg. per hundred cubic centimeters and 2 lymphocytes per cubic millimeter. Encephalograms showed slight depression of the floor of both lateral ventricles, enlargement of the basal cistern and mild general cortical atrophy.

Administration of phenobarbital, bromides and harmine had no effect on the movements. They were abolished only by deep surgical anesthesia.

At operation, on March 7, 1933, the upper cervical portion of the cord was exposed, and the foramen magnum was observed to be enlarged. The roots of the eleventh nerve were severed within the skull, and then the anterior roots, from the first to the third cervical segments on both sides. The anterior column was severed on the left between the first and the second cervical segment. Smart bleeding ensued, which was controlled by packing. The wound was closed. The patient's respirations were abolished on the left and were feeble on the right. A transfusion was given and the patient placed in a Drinker respirator. The heart ceased beating about ten hours after the operation.

Autopsy showed diffuse degeneration of the basal nuclei.

The third case was that of Morris G., a man of 56, who was referred by Dr. G. Colket Caner and Dr. Roger I. Lee. He began to have mild incoordination of the trunk and legs at the age of about 20. These symptoms had slowly progressed to involve both arms and the neck and face. The patient could walk, but only with the greatest difficulty; he could scarcely sit still in a chair, could seldom lie still and could not feed or dress himself without some assistance. Operation was undertaken with misgivings, owing to the patient's age, which was far out of the range of the others in the series, but after a long delay both the patient and his attendants agreed on it.

The operation appeared to go smoothly. First the left anterior column—corresponding to the more affected side—was cut at the level of the second cervical segment. Next, the first three anterior roots on both sides were crushed. As the patient appeared to be in excellent condition, a superficial incision was made in the right anterior column at the third cervical segment. The laminectomy wound was closed, and the spinal accessory nerve was severed on both sides through an incision along the anterior border of the sternocleidomastoid muscle.

The patient made an excellent recovery and lay relaxed in bed for the first time in years. He seemed a little restless; a few days later he was slightly disoriented and, finally, frankly delirious. The pulse and respiration began to rise, and in spite of treatment in an oxygen tent, the patient died exactly one week after operation.

Autopsy showed that the wounds were in perfect condition and that there was no infection in the lungs or elsewhere. The brain showed diffuse atrophy of the cells of the basal nuclei, without inflammatory phenomena.

In most cases in which bilateral operation has been performed, the patient's respiration has been a matter of concern for several days. Movements of the chest on the side of operation are almost always diminished or absent for from two to five weeks, and section of the

anterior roots leads to temporary weakness of the diaphragm. With the recognition of symptoms of the "progressive confusional syndrome" and the use of a respirator and transfusions as indicated, fatalities from this cause should be avoided in the future.

Transient flaccid paralyses and transient vesical and (in one case) rectal incontinence have frequently been observed. Paralysis of the bladder should be treated promptly by tidal irrigation.[20] The other untoward symptoms need no treatment, and they have never remained permanent.

Beneficial Results of the Operation.—Immediately after operation the affected extremities are almost always relaxed and motionless and sometimes paralyzed. Neither the relaxation nor the paralysis remains unchanged, however. Voluntary movement begins to return in about a month, and at the same time some tendency to abnormal movement usually makes itself manifest, but seldom to the same degree as before

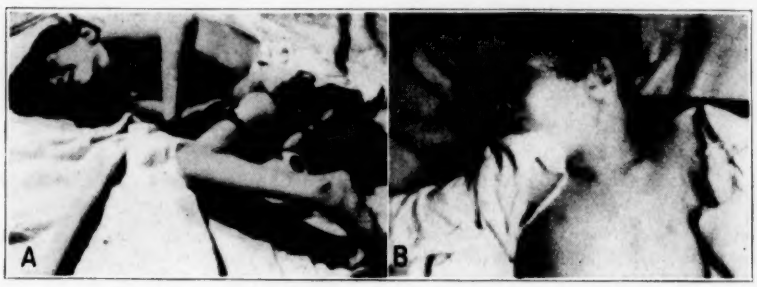

Fig. 3.—Catherine L., a feebleminded child, with bilateral athetosis. *A*, before operation, and *B*, two weeks after operation.

operation. Since the improvement is seldom more than quantitative, it is extremely difficult to evaluate in detail. One portion of the total syndrome which can be affected favorably with regularity is the torticollis. The only index to improvement in the total organism which one can give is to describe the results in terms of the activities which could be carried out before and after operation, respectively.

To begin with the lower levels of activity: Two feebleminded girls, with bilateral athetosis, torticollis and dystonia involving the face, who could not lie still in bed before the operation, were distinctly quieter, easier to take care of and apparently more comfortable afterward. In one of these cases the improvement was rather trifling, but in the other it was so substantial that the mother was extremely grateful (fig. 3 *A* and *B*).

20. Munro, D., and Hahn, J.: Tidal Drainage of Urinary Bladder: Preliminary Report of This Method of Treatment as Applied to Cord Bladders, with a Description of the Apparatus, New England J. Med. **212**:229 (Feb. 7) 1935.

Two other patients—both boys—were confined to bed with generalized athetosis but were of normal or superior intelligence. Both these patients were enabled to sit in a chair alone, which had previously been impossible. Speech was improved in both, apparently owing to better control of respiration. Although neither can feed or clothe himself, the wide, violent movements which formerly occurred have been greatly diminished. One of these patients (Tommy W.) was reported on in the first paper.[3] After five years scoliosis has developed, but the athetosis and tremor are far less marked than before operation.

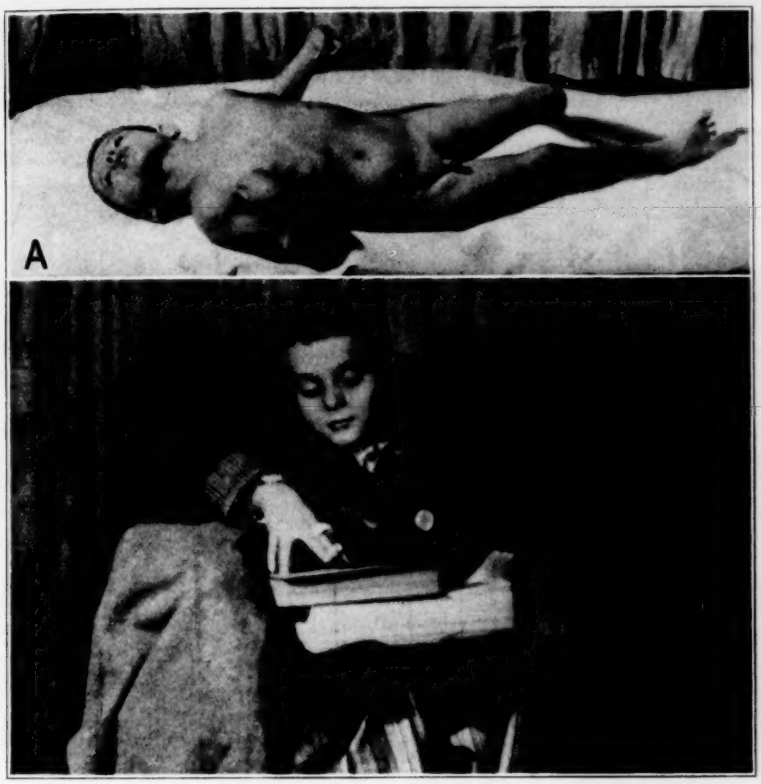

Fig. 4.—Robert H., a boy of normal intelligence, with bilateral athetosis. *A*, before operation, and *B*, three weeks after operation. In the postoperative view, the patient is attempting to write with a pencil strapped to the forefinger.

The other patient, Robert H., aged 10 years, was referred by Dr. Frank Ober. He was the second of twins, born prematurely at 7 months. He breathed well at birth but had difficulty in swallowing. He had a febrile illness at the age of 2 months. The athetoid movements began at the age of 9 months and have increased steadily. The patient had never been able to stand or walk, could not sit up unaided and had to be fed. He is apparently as bright as his normal twin, though smaller; his mental age is rated at 12 years.

Examination showed that all the muscles of the extremities, neck and face were involved in irregular bursts of contraction, causing moderately wide move-

ments of the arms and legs (fig. 4*A*), slight torticollis, grimacing and squirming of the tongue, interfering with speech. Deep reflexes could not be elicited satisfactorily. The Babinski response was negative on both sides. Electromyograms showed intermittent showers of impulses, in groups spaced about one-tenth second apart.

On Oct. 7, 1936, bilateral chordotomy was carried out at the level of the second and third cervical segments. As the patient stood this part of the operation well, the first two anterior roots on either side were crushed. During the closure, the patient's blood pressure dropped alarmingly, and a transfusion was given. The chest was paralyzed, and he had to be kept in a Drinker respirator for seventy-two hours. Catheterization was necessary. All the extremities were flaccid.

On October 25 some movement returned to the hands. Ankle clonus and a withdrawal response could be elicited. On December 3 mild athetoid movements began rather suddenly in the shoulders and upper parts of the arms, but not in the trunk or legs. On examination on May 10, 1937, the movements were found

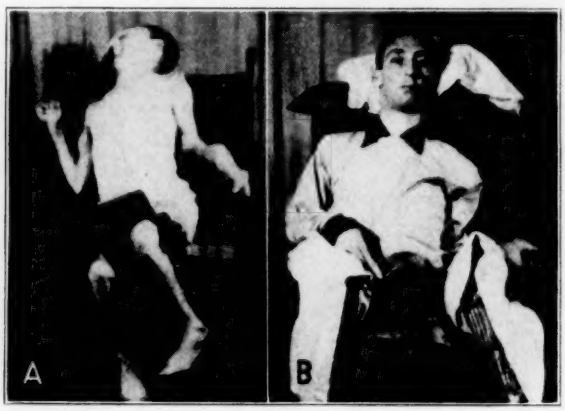

Fig. 5.—John F. *A*, before operation, and *B*, after operation.

to be not nearly as severe as before. The patient could sit up in a special chair—which was formerly impossible—and had better control of the respiratory movements (fig. 4*B*). The deep reflexes were sluggish. There was a bilateral Babinski response.

Improvement in the abnormal movements has led to a definite change in the patient's psychologic status. He is more cheerful, cooperative and hopeful and carries out his exercises better. His reading and arithmetic, formerly almost impossible because he could not fix steadily on a page, are markedly improved.

A third patient, affected with almost equally bizarre movements but able to walk a few steps with assistance and to sit with difficulty in a special chair (fig. 5*A*), can sit steadily in any chair since the operation (fig. 5*B*) and lie on his back in bed for the first time in his life. Since the wide athetotic movements in the right hand have disappeared, a definite alternating tremor has become manifest.[21]

21. Since the preceding reports were sent to press, three other patients in this general category have been operated on. All three have improved—one even more dramatically than Robert H.

A fourth patient with similar, but less pronounced, disability was able to get about with difficulty, both before and after the operation. He is distinctly more comfortable, but his range of activities has not increased. In this case there appears to be slow progression of the disease. The two familial cases (Harriet H. and Beverley H.) reported in a previous paper probably also belong in this category.

Two patients who were unable to walk before the operation can both do so now, two years later. One has returned to work after disability of three years. In both these cases the abnormal movements were confined to one leg, and operation was carried out in the thoracic region.

Walter D., aged 45, who was admitted to the Baker Memorial Hospital on May 23, 1934, was well until sixteen years before. At that time he was in an airplane accident and is said to have suffered fractures of the skull and spine. The right leg had been weak ever since, with gradually increasing athetoid movements. Thirteen months before admission he had a severe streptococcic infection of the throat. Ever since, the right leg had been in constant painful spasm and out of control. He also suffered from headaches.

Electromyograms taken with a needle electrode showed a constant series of rapid regular impulses, at the rate of 13 per second. Some consultants expressed the opinion that the spasm was hysterical, but it was impossible to produce imitation of the electromyographic record by voluntary attempts. Deep anesthesia with sodium amytal failed to abolish the tremor.

Operation was performed on June 1, 1934. The right anterior column was severed opposite the fifth dorsal vertebra. As some tremor persisted, the wound was reopened two days later and a more radical incision made.

The tremor was reduced to a mere trace, and voluntary movement was preserved; a hallucinatory psychosis developed, however, which lasted six weeks. The patient was able to walk with a cane at the time of his discharge, on August 1, and has since returned to his work of selling and servicing oil burners, but he still complains of pain in the leg and of headache.

One patient suffered chiefly from torticollis, which was practically abolished by section of anterior roots and both spinal accessory nerves. Athetosis of the left hand was relieved by section of the corresponding anterior column to such an extent that the patient can now use the hand for typewriting. These two improvements have brought about a great widening of her horizon. In a similar case, but in one in which, unfortunately, the disease appears to be progressive, the patient's handwriting is strikingly improved, and she is taking piano lessons, which were formerly impossible for her.

Of eight patients with athetosis limited almost entirely to one hand, one had only temporary improvement. In this instance, however, the disability consisted in a forced position of the hand rather than uncontrollable movement. Some diminution in the athetosis occurred in all the others. In two patients it was so slight that little advantage could be taken of it. One patient has been operated on so recently that the hand is still somewhat flaccid. In the rest useful recovery occurred, and one has returned to work.

Walter J., aged 22, who was admitted to the nonsurgical service of the Boston City Hospital on Nov. 28, 1933, was stated to have sustained a cerebral injury at birth, which left him with awkwardness and weakness of the left hand, not accompanied by atrophy or striking changes in reflexes. Seven years prior to admission, he began to have athetoid movements of the affected arm and leg, which increased to such an extent that he was unable to work.

He was reported to be below average mentally. Encephalograms showed some enlargement of the left ventricle downward, without much cortical atrophy.

Operation was performed on Dec. 21, 1933, by Dr. Walter Wegner, by whose permission the case is included in the present series. The left anterior column was incised at the third cervical segment to a depth of 3.5 mm.

The patient made an excellent operative recovery. The abnormal movements were practically abolished; normal power was retained, and the patient has since worked as a truck driver.

Physiologic Results of Section of the Anterior Columns.—There is surprisingly little disturbance of normal function from section of the extrapyramidal tracts. Patients are able to stand, walk normally and use their hands for skilled movements after the operation if they were able to do so before. The temporary loss of control of the sphincters is soon regained. There is no loss of coordination. "Forced grasping" did not develop; indeed, in some instances a spasmodic grasp was relaxed.

Little further is revealed by ordinary neurologic examination. After the shock of the operation has worn off, the deep reflexes are not exaggerated below the level of the section; the abdominal jerk is not abolished, and the Babinski and similar reflexes usually remain unchanged. When some deficit in the pyramidal tract coexists, the knee jerk may acquire a rapid, pendulous character. If the section is carried too far posteriorly, slight contralateral hemianalgesia may be produced, but it has been permanent in only two cases. No disturbances attributable to destruction of the spinocerebellar pathways are observable. Temporary vasodilatation on the side of the operation was observed in a few instances, but it was not permanent, and no other gross interruption of function of the viscera was observed.

Patients Not Relieved by Section of the Anterior Column.—In four cases apparently not belonging to the athetoid group, section of the anterior column produced neither benefit nor exacerbation at any time. Two of these were typical instances of juvenile paralysis agitans, and one was reported in a previous paper.[3] In a third, there was a history of encephalitis, followed by a coarse generalized tremor, tossing movements of the head and spasmodic opening of the mouth. Encephalograms showed enlargement of the ventricles and basal cistern. In a fourth, that of Barbara G., the symptoms came on after injury at birth and consisted of a rhythmic, alternating rotatory movement of the left arm, which was increased by attention (fig. 6). Encephalograms revealed nothing abnormal. In none of these cases was there the slightest change in the patient's condition, either for better or for worse, after section of the anterior column.

It is to be noted that the condition followed encephalitis in two instances and was typical of parkinsonism in a third. In the last case

electromyograms showed a slow, regular rhythm suggestive of that seen in paralysis agitans, which should have been taken as contraindication to operation.

COMMENT

The therapeutic results speak for themselves. There have been deaths which should be avoidable in the future, but no other unfavorable results. If the cases of parkinsonian rather than of athetoid movements are eliminated—as they should by proper study—a large proportion of patients operated on should show some benefit and some of them considerable improvement. Operation should be considered not as an alternative to reeducation or the use of appropriate drugs but rather as an adjunct.

From the physiologic point of view, the results are interesting in several respects. First, they demonstrate the fact that the fibers running in the prepyramidal region and the anterior column may be

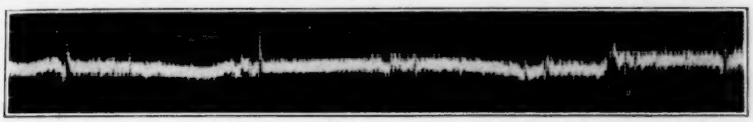

Fig. 6.—Electromyogram of Barbara G., taken with band electrodes. There are regular bursts of impulses, at a rate of 7 per second, resembling those seen with paralysis agitans. The tremor was not influenced by chordotomy.

severely damaged, and perhaps totally destroyed, without gross impairment of the subject's ability to stand, walk, control the sphincters and coordinate. No striking permanent change in reflexes has been observed. Thus it will be seen that the effects of section of the anterior column are in no way comparable to those of a lesion of the premotor cortex.

Second, even if one admits that relief is often incomplete, it appears that many of the impulses mediating the abnormal movements of athetosis must be transmitted by neurons lying in the anterior columns. The movements which persist after operation may be transmitted by fibers lying deeper than it is safe to cut—for example, mingled with the respiratory tract or in the pyramidal tract. This suggests that the abnormal impulses arise in an irritated or periodically discharging focus, probably subcortical.

Third, it seems safe to predicate that tremors of the paralysis agitans type are not mediated (nor inhibited) by the extrapyramidal tracts. They are, therefore, presumably transmitted by the pyramidal tract or conceivably are due to absence of "pyramidal" inhibition.

SUMMARY

1. The clinical phenomena of the "athetoid syndrome" are described, and the criteria by which it may be distinguished from other diseases characterized by involuntary movements are discussed.

2. A series of twenty-three patients suffering from this syndrome who were subjected to section of the anterior column of the spinal cord is reported. The operation is designed to sever the extrapyramidal motor fibers, which apparently transmit the abnormal movements causing athetosis.

3. There have been three deaths in the series, from causes which should be avoidable in the future. There have been no other permanent ill effects.

4. Seventeen of the survivors have shown varying degrees of improvement for periods up to five years. One can lie quietly in bed, which was formerly impossible; three have been enabled to sit up in a chair and two to walk, and three have returned to work. In the rest the result was variable and, while often gratifying to the patient, did not permit an increase in activities.

5. A group of four cases in which there was no result from the same operation is analyzed. In these the tremor was of a different type, of which paralysis agitans is a familiar example.

6. The light which these operations throw on the physiologic rôle of the extrapyramidal tract and on the mechanism of the dyskinesic diseases is discussed.

ABSTRACT OF DISCUSSION

DR. ERIC OLDBERG, Chicago: To an audience, the continuous, uncontrollable movements of the extremities and the hideous grimacing are likely to appear so grotesque as to give the impression that the state of the human material involved is too poor and defective to be worth alleviating. This is not the fact, however. Many of these persons with congenital spasticity and athetosis have quite normal intellects and could be made much more useful to themselves and to society if relieved from their torments; in addition, these extraneous movements are often exquisitely painful. This is true also in other conditions, such as in certain cases of advanced multiple sclerosis, in which the operation is of equal value.

Until recently there were but two approaches to such a problem—amputation of the offending extremity, which is mutilating, and sympathectomy, which is neither rational nor efficacious. Two new procedures have since been evolved—ablation of the premotor cortex in the brain and section of the extrapyramidal tracts in the spinal cord. Both are still in the empirical stage, especially the latter, but they are scientifically reasoned and are effective.

I prefer section of the extrapyramidal tracts. The mortality and the morbidity risk seem to me less than that of an intracranial operation in which an area so closely related by position and blood supply to the rolandic area is extirpated. My experience has been limited to section of the extrapyramidal pathways, and I have operated on ten patients thus far, with no mortality and no morbidity. Several

of these persons could walk, and I should have hesitated to bank on my ability to ablate an isolated arm area in the premotor region without altering the function of any contiguous cortex. The results have been gratifying. The usual postoperative picture is that of instantaneous and spectacular flaccidity and relaxation on the side of operation, without any permanent motor loss. After an interval of several months, the spasticity at least partially returns, but the extraneous movements (and attendant pain, if present) remain greatly diminished or absent. This has been particularly true in two patients with advanced multiple sclerosis and marked unilateral painful athetosis, one of whom has now had relief for over two years. On the other hand, the operation has proved to be without value in two postencephalitic patients with marked painful unilateral tremor. I have performed one bilateral chordotomy, but I should not do it again, at least at one sitting, because of the alarming transitory respiratory depression. I wish to congratulate Dr. Putnam on a contribution which I think is of immense and, as yet unrealized, clinical and experimental importance.

Dr. John F. Fulton, New Haven, Conn.: I wish to say a few words about the physiologic basis of this procedure. From the point of view of mechanism, the underlying symptomatology of cerebellar lesions is similar to that exhibited by the extrapyramidal choreiform syndrome just described. The point of similarity is this: If the cerebellum is completely destroyed, the resulting symptoms clearly arise from the activity not of the cerebellum but of other parts of the nervous system; in the case of a cerebellar lesion, the activity emanates primarily from the cerebral cortex. Kinnier Wilson, realizing the similarity between the mechanism operating in cases of cerebellar lesion and the mechanisms in disease of the basal ganglia suggested that the symptoms are to be looked on as due primarily to the activity of cerebral levels in the absence of a subcortical mechanism and that, therefore, the symptoms cannot be looked on as due to the injured basal ganglia, for these have been largely destroyed. Kinnier Wilson therefore proposed the hypothesis that the motor projections from the hemisphere are the basis of these involuntary movements.

One would like, therefore, to know just what projections are responsible. Dr. Oldberg has mentioned the fact that if the extrapyramidal projections from Brodmann's area 6 are destroyed, there appears to be amelioration in certain cases. Horsley's original procedure of extirpating the motor area itself (area 4 of Brodmann) diminishes involuntary movements, but it also causes voluntary paralysis.

Dr. Putnam has given evidence that if one destroys the extrapyramidal projections as they finally reach the cord, there is also improvement. One would like to know whether the improvement which Dr. Putnam has described is due to destruction of what remains of the extrapyramidal system or to interruption of impulses arising ultimately at the cortical level but traveling along extrapyramidal paths in the cord. Personally, I am inclined to sympathize with the theory of Kinnier Wilson, and I should like to see further observations made on the effects of specific cortical lesions in these conditions; for this seems to me a more logical point of attack if Kinnier Wilson's theory is valid. I hope in time that this type of experimentation will be reported here and compared with the procedure which Dr. Putnam has just described.

Dr. Winthrop M. Phelps, Baltimore: Dr. Putnam asked me the other day in what cases of this sort I thought operation would be proper. I am unable to answer that question. It is interesting that in the general group of crippled children those with neuromotor handicaps are generally divided into two groups:

on the one hand, children who have had infantile paralysis and, on the other, apparently all the others with what is called a spastic condition. This is the general division which one sees in the various orthopedic sections of the departments of health throughout the country that handle crippled children, and it is interesting to make a survey of the group with spastic disturbances.

When this is done it is found that approximately 40 per cent of the children with this condition are truly spastic in the sense that they have evidence of motor difficulty of the pyramidal type.

Another 40 per cent is in the group with conditions covered by the term athetosis. By that I mean pure involuntary motion of all speeds and sorts except the rhythmic type seen in tremor. There is then left 20 per cent of the children of this group, whose conditions are hard to classify. Their symptoms consist of tremors, primary incoordination, ataxias and all sorts of peculiar conditions.

In the groups of 40 per cent with athetosis, which probably will surprise one by its size, there are many children who are tense with voluntary spasm but who try to control the athetosis, so that they are almost always passed over as being spastic. It is almost impossible to separate the two except by careful examination of the reflexes. Even then, in the group with athetosis one finds that the constant athetoid motions reenforce the reflexes and the apparently hyperactive knee jerks to such an extent that sometimes it is necessary to repeat the tests for reflexes a great many times.

If one of a series of reflexes is obtained in which there is no hyperactivity the disease is not explainable on the basis of pyramidal disturbance. In many children with athetosis the disease is very mild and, with retraining over a period, can be almost cured. Athetosis can be much diminished by retraining, and in some cases practically eradicated, but the difficulty with the usual retraining is that the children are all grouped as spastic and the same type of retraining is given to the patients with true spasticity as is given to those with athetosis, primary incoordinations and tremors; the results, of course, are not as good as they might be.

Dr. Putnam's work is interesting, important and extremely useful in the severe degrees of the disease. Obviously, if it takes twenty years of retraining to diminish athetosis by 50 per cent, it is not worth while; the only answer I can give to the question of which patients should be operated on is that the degree of severity and the length of the period of retraining must be the primary considerations.

DR. TRACY J. PUTNAM, Boston: I wish first to pay tribute to the work which Dr. Phelps and his associates have done with some patients in this group and to say that I do not think that any type of operation should be considered exactly as a competitor to retraining. The two can profitably be made to cooperate; as a matter of fact, most of the patients will require retraining after the operation, but retraining will be carried out with far greater ease than before. The patients have less to contend with, and lightening the burden has made possible much more rapid progress.

I wish to emphasize what Dr. Phelps has said about the necessity of making a better classification of the group with so-called spastic conditions. The subject needs to be reopened and reclassification made.

I am grateful to Dr. Fulton for this review of the physiology of athetosis. So far as I know, no cortical fibers descend in the anterior column. It is striking that in cases of athetosis in which autopsy has been performed no degenerations

have been observed in the anterior column, though they may occur in the pyramidal tract. Under these cirmcumstances, it is reasonable to believe that the impulses come over the extrapyramidal tracts.

Any discussion of this problem should include a sharp differentiation between the parkinsonian and the athetoid syndrome. I did not have time to refer to the fact that my experience with patients showing real parkinsonian tremor and rigidity has been similar to Dr. Oldberg's. I have operated on four patients that might be included in this class, with no benefit and, what to me is equally surprising, with no intensification of the syndrome; it seems fair to conclude, therefore, that the physiology of the two conditions is fundamentally different, a point which has not been sufficiently emphasized in previous discussions of the physiologic aspect.

OXYGEN AND CARBON DIOXIDE CONTENTS OF ARTERIAL AND VENOUS BLOOD OF SCHIZOPHRENIC PATIENTS

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That schizophrenia is a disease primarily due to disturbances of organic, as opposed to psychologic, functions has frequently been postulated. Two of the chief theories proposed to explain this disorder are, first, that the distortion of function is due to the presence of toxic substances, and, second, that the trouble arises from deficient oxidation in the cells of the body and especially in those of the brain. This paper is concerned with the second of these theories. Previous investigations have indicated that the oxygen consumption in schizophrenic patients is significantly lower than that in normal subjects—a finding that is presumptive evidence in support of the second theory.[1]

As part of the program of study of the organic functions in schizophrenia, the gases of both arterial and venous blood were determined by the manometric method of Van Slyke. The data recorded here were obtained by combining the earlier material obtained in the "seven months' study"[2] with that secured in a later investigation in which paired normal and schizophrenic subjects were subjected to a similar, but shorter, series of tests. In this investigation there were secured for the first time values on gases of the arterial blood in a sufficient number of normal subjects for an adequate statistical analysis of the various relationships between the gases of the arterial and those of the venous blood. The data on the normal subjects have been considered in another report.[3]

This investigation was aided by a grant from the Rockefeller Foundation.

From the Memorial Foundation for Neuro-Endocrine Research and the Research Service, the Worcester State Hospital.

1. Hoskins, R. G.: Oxygen Consumption ("Basal Metabolic Rate") in Schizophrenia, Arch. Neurol. & Psychiat. **28**:1346 (Dec.) 1932.

2. Hoskins, R. G.; Sleeper, F. H.; Shakow, D.; Jellinek, E. M.; Looney, J. M., and Erickson, M. H.: A Cooperative Research in Schizophrenia, Arch. Neurol. & Psychiat. **30**:388 (Aug.) 1933.

3. Looney, J. M., and Jellinek, E. M.: The Oxygen and Carbon Dioxide Content of the Arterial and Venous Blood of Normal Subjects, Am. J. Physiol. **118**: 225 (Feb.) 1937.

PREVIOUS STUDIES

A search of the literature yielded little information concerning the gaseous content of arterial and venous blood in schizophrenic patients. Segal and Hinsie [4] studied the problem in 14 markedly cyanotic patients with dementia praecox. They found that the mean value for arterial oxygen was 18.13 volumes per cent, with a range of from 13.43 to 22.5 volumes, although in 1 case only was it below 17.41 volumes. For venous oxygen the mean was 9.59 volumes, with a range of from 4.48 to 14.2 volumes. The carbon dioxide content of the arterial blood ranged from 44.51 to 52.8 volumes, with a mean of 50.12 volumes, and that of the venous blood, from 51.17 to 60.69 volumes, with a mean of 55.89 volumes. The values are all within normal limits except that for venous oxygen, which is lower than the value usually given as normal, i. e., 14 volumes per cent. However, the figures which Segal and Hinsie obtained for 2 normal persons were both lower than this mean—in 1 case, 8.27 volumes per cent, and, in the other, 6.84 volumes.

Myerson and Halloran,[5] in a study of the gaseous content of blood taken from the carotid and brachial arteries and from the internal jugular and basilic veins of 20 schizophrenic patients, obtained the following results: In 7 cases the average carbon dioxide content of blood from the carotid artery was 50.41 volumes per cent, and the average oxygen content, 17.69 volumes per cent. In 19 cases blood from the internal jugular vein contained 56.28 volumes per cent of carbon dioxide and 11.91 volumes of oxygen. For blood from the brachial artery and the basilic vein in 20 cases the figures were 49.76 and 54.83 volumes, respectively, for carbon dioxide and 17.46 and 13.64 volumes for oxygen. It will be noted that the mean value for the oxygen content of blood taken from the basilic vein was greater than that obtained by Segal and Hinsie but that the blood from the internal jugular vein, although having a higher oxygen content than that reported by these investigators, still showed a subnormal value. The figures of Myerson and Halloran for venous oxygen ranged from 7.72 to 17.74 volumes per cent for blood from the internal jugular vein and from 7.43 to 17.69 volumes for blood from the basilic vein. In only 6 of the 39 determinations was the value below 10 volumes per cent.

Lennox [6] determined the oxygen and carbon dioxide contents of the blood of a large number of patients, most of whom were subject to epilepsy. He found that the arterial blood of 105 patients gave a mean value of 49.37 volumes for carbon dioxide and 18.84 volumes for oxygen. The venous blood showed marked variability in both the oxygen and the carbon dioxide content, depending on the site of puncture. The lowest value for venous oxygen was given by blood from the internal jugular vein, being 12.38 volumes per cent; the highest content was obtained in blood from the external jugular vein, with a value of 17.29 volumes. The blood from the cubital vein showed an oxygen content of 13.6 volumes per cent, and that from the femoral vein, of 14 volumes. The carbon dioxide content varied in the reverse direction, the values being 51.3 volumes for the external jugular vein, 53.3 volumes for the femoral vein, 53.46 volumes for the cubital vein and 55.32 volumes for the internal jugular vein.

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4. Segal, L., and Hinsie, L. E.: The Cyanosis of Dementia Praecox, Am. J. M. Sc. **171**:727, 1926.

5. Myerson, A., and Halloran, R. D.: Studies of the Biochemistry of the Brain Blood by Internal Jugular Puncture, Am. J. Psychiat. **10**:389, 1930.

6. Lennox, W. G.: The Oxygen and Carbon Dioxide Content of Blood from the Internal Jugular and Other Veins, Arch. Int. Med. **46**:630 (Oct.) 1930.

METHODS

In the present study the results for the gases of the venous blood represent samples taken from 112 patients and 67 normal subjects serving as controls. The blood was taken under basal conditions from the median basilic vein. A tourniquet was used to facilitate the entrance of the needle into the vein and was immediately released, and from thirty to sixty seconds was allowed to elapse before the sample was drawn. That this interval was sufficient to prevent any significant changes as the result of stasis was shown in a study by Looney and Childs.[7] The blood was collected and stored according to the technic described by them. The samples of arterial blood were drawn immediately preceding those of venous blood, after preliminary anesthesia with procaine hydrochloride. The radial artery was utilized in the earlier study of the patients and the brachial artery in the later study of both the patients and the normal subjects. In the merged sample values for arterial blood were obtained for 112 schizophrenic patients and 29 normal subjects.

TABLE 1.—*Constants for Frequency Distributions, Expressed in Volumes Per Cent*

Group	No. of Subjects	Minimum, Vol. Per Cent	Maximum, Vol. Per Cent	Mean and Standard Error	Standard Deviation and Standard Error
		Arterial Oxygen			
Merged sample—patients	112	11.3	22.3	18.8±0.21	2.2±0.15
Comparative study—normal controls	29	10.5	22.8	19.0±0.47	2.5±0.33
		Venous Oxygen			
Merged sample—patients	112	4.1	17.9	9.8±0.28	2.9±0.20
Merged sample—normal controls	67	4.0	17.5	10.6±0.36	2.9±0.25
		Arterial Carbon Dioxide			
Merged sample—patients	112	42.5	62.8	49.2±0.29	3.0±0.20
Comparative study—normal controls	29	40.8	57.4	49.9±0.51	2.7±0.36
		Venous Carbon Dioxide			
Merged sample—patients	112	47.5	76.4	57.8±0.36	3.7±0.25
Merged sample—normal controls	67	49.7	63.5	57.8±0.35	2.8±0.24

Justification for merging the data obtained from the various studies was established by careful statistical analysis. It was shown that the results obtained for the normal subjects at different times were not appreciably different as regards the means and the standard deviations. Similarly, the means and standard deviations were found to be essentially the same in each of the various groups of schizophrenic patients, indicating that each subsample of patients was drawn from a common population. This agreement in the samples taken at different periods gives considerable weight to the fact that the values obtained in these studies may be considered as representative of the normal and the patient population, respectively. These merged samples have been used not only for the calculation of constants for frequency distributions but for the various correlations existing among the volumes of the gases.

RESULTS

In table 1 are listed the constants for the distributions of arterial and venous gases for the patients and for the normal subjects used as controls.

7. Looney, J. M., and Childs, Hazel: A Comparison of the Methods for the Collection of Blood to Be Used in the Determination of Gases, J. Biol. Chem. **104**:53, 1934.

The table shows that there are no statistically significant differences between the mean or the standard deviations for the schizophrenic and those for the normal subjects except the difference between the standard deviations for venous carbon dioxide. As indicated in figure 1 *A* by the superimposed frequency polygons for normal subjects and patients, the distributions for venous oxygen are practically identical.

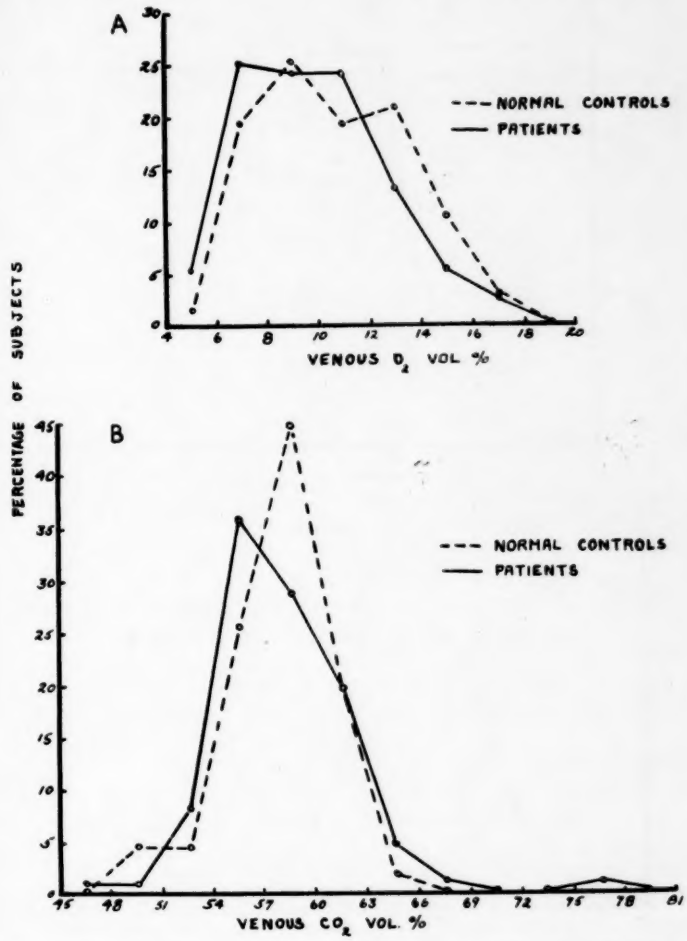

Fig. 1.—Distributions in 67 normal and 112 schizophrenic subjects for (*A*) venous oxygen and (*B*) venous carbon dioxide.

In the case of venous carbon dioxide, plotted in figure 1 *B*, the distributions, despite the nearly identical means and standard deviations, appear to show certain essential differences. The mean value has been raised by the presence of a few extremely high values, although the modal value is considerably lower in the patients than in the normal subjects. Statistical analysis confirms the impression

given by the frequency polygons, namely, that the difference between the two distributions of venous carbon dioxide is at least of borderline significance. It is reasonable to state, therefore, that the value for venous carbon dioxide for patients is usually lower than that for normal subjects used as controls, in spite of the equal means.

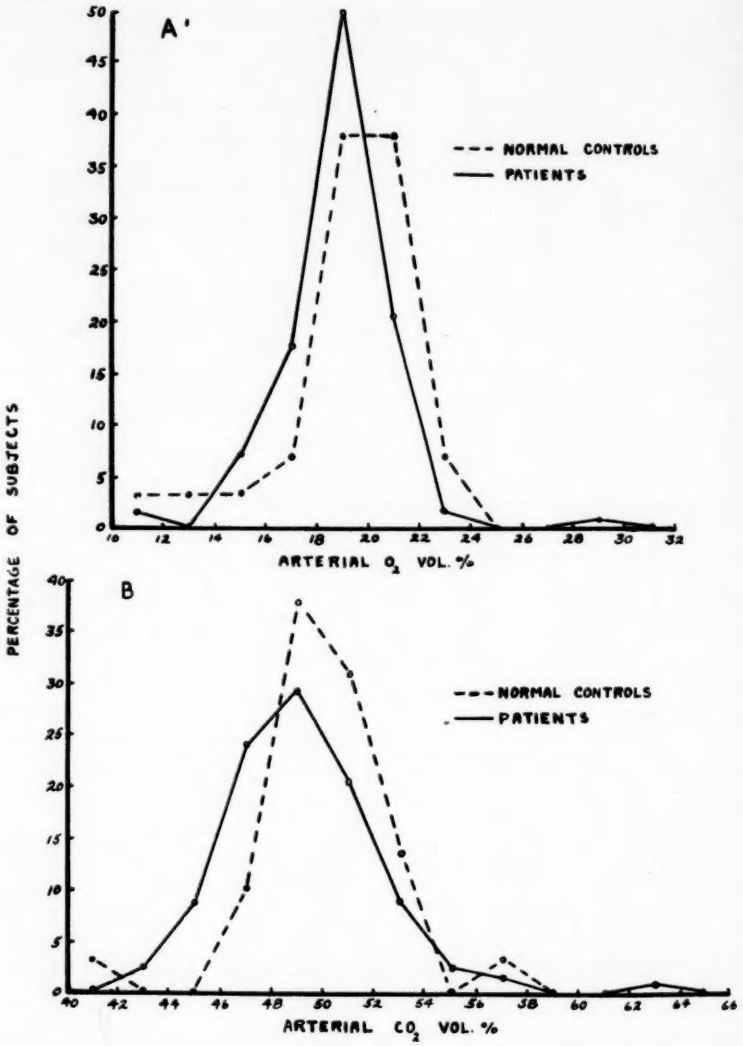

Fig. 2.—Distributions in 29 normal and 112 schizophrenic subjects for (*A*) arterial oxygen and (*B*) arterial carbon dioxide.

On the arterial side no significant differences between the normal and the schizophenic subjects were found for either the oxygen or the carbon dioxide content. The frequency polygons for these gases are given in figure 2 *A* and *B*.

When the mean values were determined for the gases of the blood according to psychiatric subgroups, no significant differences were found.

The mean difference between the arterial and the venous oxygen level for the 30 patients making up the comparative study group was 9 ± 0.59 volumes per cent, with a standard deviation of 3.2 ± 0.42 volumes per cent. For the 29 normal subjects in this study used as controls, the mean was 8.8 ± 0.59 volumes per cent, and the standard deviation, 3.1 ± 0.4 volumes. The mean differences between the carbon dioxide levels were 8.1 ± 0.55 volumes per cent for the patients and 8.4 ± 0.63 volumes for the controls. The standard deviations were 3 ± 0.39 and 3.3 ± 0.45 volumes per cent, respectively. The range in each instance extended from 2.5 to 14.5 volumes per cent, except that in case of the differences in carbon dioxide in the normal subjects the minimum value was 0.5 volume and the maximum 18.5 volumes per cent. The differences between the patients and the normal subjects are not significant, but it is of interest to note that the patients produced a smaller volume of carbon dioxide for the same amount of oxygen than the normal subjects. The respiratory quotients calculated from these values were 0.9 for the patients and 0.95 for the controls and indicate the combustion in the tissues of a larger proportion of carbohydrate in the normal subjects than in the patients.

Studies of the relationship obtaining between the gases of the venous blood reveal more important differences between patients and subjects serving as controls than between the actual levels of the gases.

Insignificant coefficients of correlation were obtained for the relationship between arterial and venous oxygen for both the patients and the controls. This demonstrates that under basal conditions the level of oxygen in the venous blood is independent of that in the arterial blood. The oxygen content of the venous blood is primarily controlled by the demand of the tissues for oxygen and the velocity of the blood through them. It should be noted in this connection that the total volumes of blood is smaller [8] and that the velocity is slower [9] in the patients than in the normal subjects used as controls. One would expect, then, that the oxygen content of venous blood in the patients would be markedly lower than that in normal subjects, as the oxygen levels for arterial blood are approximately the same in both groups. As there is no significant difference between the oxygen content of venous blood of the controls and that of the patients, it appears that in the patients the utilization of oxygen by the tissues is subject to some interference. In the patients the process of oxygenation of the blood in the lungs and the supply carried to the tissues seem to be adequate.

In the case of carbon dioxide, we find that for the normal subjects the level in the venous blood is unrelated to that in the arterial blood, as the coefficient of correlation is practically zero, while for the patients a relatively high relationship exists, with a correlation coefficient of 0.84. Thus, for the control subjects one is not able to predict the value of the venous carbon dioxide when the arterial level is known, but for the schizophrenic patients there is a change of 1 volume per cent in the carbon dioxide content of venous blood for each unit of change on the arterial side.

With regard to the correlation between the oxygen and the carbon dioxide content of venous blood, we find that the normal subjects, with a correlation coefficient of —0.76, show a significantly higher interdependence of the two gases

8. Looney, J. M., and Freeman, H.: Volume of Blood in Normal Subjects and in Patients with Schizophrenia, Arch. Neurol. & Psychiat. **34**:956 (Nov.)1935.

9. Freeman, H: The Arm-to-Carotid Circulation Time in Normal and Schizophrenic Subjects, Psychiatric Quart. **8**:290, 1934.

than the patients, with a correlation coefficient of —0.47. The same discrepancy between the patients and the control subjects occurs on the arterial side, though it is not so marked. The correlation coefficients were —0.17 for the patients and —0.54 for the normal subjects.

A better understanding of the significance of these findings can be obtained by consideration of the variation in the gases of the blood in the individual subject. In correlating repeated readings of the gases of the blood of the same person, it was found that patients showed a fair degree of consistency for arterial and venous carbon dioxide and arterial oxygen but practically no consistency for venous oxygen. On the other hand, the normal subjects showed no consistency for either arterial or venous carbon dioxide and slight consistency for arterial and venous oxygen.

The total effect of these relations appears to be that the patients have a much greater rigidity in the carbon dioxide system. This is indicated by the fairly constant relation between the arterial and the venous carbon dioxide level and its moderate consistency on repeated readings in the same subject. This rigidity in the physiologic functions of schizophrenic patients has been noted before in the relationship between the systolic and the diastolic blood pressure, reported by Hoskins and Jellinek,[10] and has been interpreted as indicative of failure of the sympathetic nervous system in the homeostatic control of body functions. For the same relationships the normal subjects show no consistency. In contrast to this, the normal subjects show a much higher dependency between the level of oxygen and that of carbon dioxide than the patients. In other words, production of carbon dioxide in normal subjects is a great deal more dependent on the oxygen intake than in schizophrenic patients, at least in the basal state. This difference between the two groups is statistically highly significant.

The schizophrenic patient converts less of the oxygen into carbon dioxide than does the normal person, so that in the schizophrenic patient only 12 per cent of the variation in venous carbon dioxide is explained by the changes in venous oxygen, while in the normal subject three times as much of the variation is accounted for in this manner. On the arterial side, the difference between schizophrenic and normal subjects in the relationship of carbon dioxide and oxygen is not statistically significant, but this is probably due to the smallness of the control sample. The difference between the respiratory quotients of the two groups confirms this finding in regard to the production of carbon dioxide, as the value for the normal subjects is higher than that for the patients.

On the whole, it appears that in the basal state the schizophrenic patient has an adequate mechanism for obtaining oxygen and transporting it to the tissues but that he is handicapped in some way, so that the utilization of this oxygen by the tissues is deficient. We shall attempt to test this point experimentally by subjecting patients to a lowered oxygen tension and following the gases in the blood.

SUMMARY

The venous levels of carbon dioxide and oxygen were determined in 112 schizophrenic and 67 normal subjects. The arterial gases were likewise determined in the same group of patients but in only 29 normal subjects.

10. Hoskins, R. G., and Jellinek, E. M.: The Schizophrenic Personality with Special Regard to Psychologic and Organic Concomitants, A. Research Nerv. & Ment. Dis., Proc. **14**:211, 1933.

No significant differences were found in the levels of these gases in the samples of blood from the two groups except in the values for venous carbon dioxide, which, although they have the same mean, have an essentially different distribution. The values, expressed in volumes per cent, were as follows: For the patients the mean for arterial oxygen was 18.8 volumes, for arterial carbon dioxide 49.2 volumes, for venous oxygen 9.8 volumes and for venous carbon dioxide 57.8 volumes. For the normal subjects the mean for arterial oxygen was 19 volumes, for arterial carbon dioxide 49.9 volumes, for venous oxygen 10.6 volumes and for venous carbon dioxide 57.8 volumes.

Some of the correlations between the gases were significantly different in the two groups. The greatest difference was found in the relationship between the carbon dioxide content of the arterial and that of the venous blood. In the patients there was a high degree of dependency, as indicated by the correlation coefficient of 0.84, while in the normal subjects there was no relationship, as the correlation coefficient was practically zero. A significant difference was also found for the correlation between the oxygen and the carbon dioxide level of the venous blood, as there was a much greater dependency in the normal than in the schizophrenic subjects.

CONCLUSIONS

There is no significant difference between normal and schizophrenic patients in the levels of oxygen in the arterial and the venous blood or in the carbon dioxide content of the arterial blood. The distribution of carbon dioxide in patients is essentially lower than that in normal subjects.

There are significant differences between the two groups with regard to the mechanisms governing the interrelationships between the gases.

Schizophrenic patients do not differ from normal subjects as far as the supply of oxygen to the body tissues is concerned but show a certain degree of dysfunction in its utilization.

The carbon dioxide mechanism is more rigid and static in schizophrenic than in normal subjects.

LIPOID CONTENT OF THE BLOOD IN DEFICIENCY DISEASES AND DURING DEMYELINIZATION OF THE NERVOUS SYSTEM

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It has been repeatedly demonstrated that prolonged subsistence on diets deficient in one or more of the vitamins A, B_1 and B_2 (G) results in severe disorders of the nervous system both in animals and in man.[1] It is also recognized that other factors, such as lack of the intrinsic factor of Castle, difficult absorption and toxic factors, may make certain persons peculiarly susceptible to the development of disorders of the nervous system while living on diets only moderately deficient in vitamins A, B_1 and B_2 (G). In man, examples of the effect of a deficiency in one vitamin only are rarely encountered, particularly in the northeastern United States, where the present study was made.[2]

Consequently, an estimate of the various dietary factors which have produced a particular syndrome encountered in the clinic has to be arrived at by indirect methods. The history of the diet is helpful but unreliable, and usually reveals that the patient has been subsisting on a variable diet deficient in a number of respects. Much can be learned from the analogous nature of the clinical syndromes to that of syndromes observed in animals in which the deficient factor was known. The presence of certain symptoms which cannot be accounted for by other diseases may be taken as evidence of deficient nutrition. These may be summarized as follows: disorders of the nervous system, par-

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From the Department of Psychiatry, the Yale University School of Medicine.

1. (*a*) Cowgill, G. R.: Vitamin B, New Haven, Conn., Yale University Press, 1934. (*b*) Zimmerman, H. M.: Lesions of the Nervous System in Vitamin Deficiency: I. Rats on a Diet Low in Vitamin A, J. Exper. Med. **57**:215, 1933. (*c*) Zimmerman, H. M., and Burack, E.: Studies on the Nervous System in Deficiency Diseases: II. Lesions Produced in the Dog by Diets Lacking the Water-Soluble, Heat-Stable Vitamin B_2 (G), ibid. **59**:21, 1934. (*d*) Zimmerman, H. M.; Cohen, L. H., and Gildea, E. F.: Pellagra in Association with Chronic Alcoholism, Arch. Neurol. & Psychiat. **31**:290 (Feb.) 1934. (*e*) Gildea, M. C. L.; Castle, W. B.; Gildea, E. F., and Cobb, S.: Neuropathology of Experimental Vitamin Deficiency, Am. J. Path. **11**:669, 1935. (*f*) Minot, G. R.; Strauss M. B., and Cobb, S.: "Alcoholic" Polyneuritis: Dietary Deficiency as a Factor in Its Production, New England J. Med. **208**:1244 (June 15) 1933. (*g*) Spies, T. D.: Observations on the Treatment of Pellagra, J. Clin. Investigation **13**:807, 1934.

2. Aykroyd, W. F.: Pellagra, Nutrition Abstr. & Rev. **3**:337, 1933. Cowgill.[1a]

ticularly those indicative of polyneuritis, paresthesias of the extremities, tenderness over the nerve trunks, sensory impairment and paralysis and, less frequently, disturbances of the brain and cord; anemia, either microcytic or macrocytic; lesions of the skin—dermatitis with scaling and pigmentation, usually of exposed areas—and, finally, a red, "beefy" tongue or a smooth tongue with atrophic papillae. The fact that patients with these symptoms recover if the disease is not too far advanced when given an adequate diet supplemented with vitamin concentrates lends additional evidence in favor of the rôle played by lack of these factors in producing such syndromes.

Milbradt [3] reported that dietary deficiency in vitamins B_1 and B_2 (G) decreases the amount of lipoids in the blood, while Sure, Kik and Church [4] reported no effect. Vitamin A deficiency reduces the cholesterol content of the blood, according to Collazo, Torres and Sánchez Rodríguez [5] and Ralli and others,[6] while Jusatz [7] found the reverse to be true. In a previous paper Man and Gildea [8] presented evidence to the effect that prolonged and severe undernutrition usually depletes the serum lipoids in man.

In the present investigation the serum lipoids of patients suffering from severe symptoms of deficiency disease have been studied. Some of these patients had not had much loss of weight because their caloric intake had been adequate, although the diet was deficient in vitamins, while the rest were suffering from deficiency of both calories and vitamins. A comparison of these two groups should offer the opportunity to determine the relative effects on the serum lipoids of vitamin deficiency alone and a combined deficiency in calories and vitamins.

Attention has also been paid to the question whether a process of relatively rapid disintegration of the nervous system, and particularly of the myelin sheaths, may not, temporarily at least, be accompanied by a rise in the lipoids of the blood.

METHODS AND MATERIAL

All the samples of blood were taken from a vein in the arm when the patients were in the postabsorptive state. Serum from these samples was analyzed for total fatty acids, phosphatide phosphorus, cholesterol and proteins by methods

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4. Sure, B.; Kik, M. C., and Church, A. E.: Effect of Vitamin B Deficiency on Lipid Metabolism, Proc. Soc. Exper. Biol. & Med. **29**:848, 1932.

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previously described.[9] The errors in these methods and the range of normal values have been discussed in former papers.[10]

All twelve patients in this study had shown various symptoms of deficiency disease after prolonged subsistence on bizarre and deficient diets. Repeated determinations of the serum lipoids were made on eight of the patients during the progress of the disease. Four patients in the series died, and it was possible to confirm the clinical findings by observations at necropsy.

The term "undernourished" has been used to describe only states of unquestionable emaciation, in which the skin was loose and wrinkled. Statements of the patients proved so uncertain as to the previous weight and actual loss of weight that figures have not been included in the table. Degrees of undernutrition have been recorded comparatively in terms +++, ++ and +; the symbol 0 has been used to indicate no undernutrition. The relative severity and the presence of polyneuritis and lesions of the skin and mouth have been expressed in the table in a similar fashion. Detailed descriptions of the patients have been presented in summaries of the records at the end of this paper.

OBSERVATIONS

The results are analyzed briefly in the table. In the first group, seven patients had severe undernutrition and a number of symptoms of deficiency disease. Five of these persons made a good recovery on a high vitamin diet supplemented with concentrates of vitamins B_1 and B_2 (G). Necropsies[11] were obtained on the two patients who failed to respond to treatment, and evidences of marked demyelinization of the peripheral nerves and tracts of the cord were observed. It is noteworthy that in all but one patient the value for cholesterol was below the low normal limit, of 150 mg. per hundred cubic centimeters. Even in this exception it was within the low normal range. The total fatty acids were low in four patients and close to the median figure for normal in three others.

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11. Dr. Harry M. Zimmerman, of the department of pathology, made the studies of the pathologic changes in these patients.

Case No.	Age of Patient, Yr.	Date	Clinical Condition: Polyneuritis, Degree	Red Blood Cells, Millions per Cu.Mm.	Lesions of Skin	Lesions of Mouth	Degree of Undernutrition	Serum: Total Fatty Acids, M.Eq.	Cholesterol, Mg. per 100 Cc.	Phosphatide Phosphorus, Mg. per 100 Cc.	Total Protein, Percentage	Comment; Course of Disease
I. Patients with Polyneuritis and Undernutrition												
1	56	8/12/36	+	3.20	+	+++	++	8.5	123	7.4	4.76	Chronic alcoholism; had eaten little food for 8 mo.; acute symptoms from 3-4 wk.; good recovery
		8/25/36	..	....	..	++	++	10.5	114	6.4	6.02	
		9/ 1/36	..	4.31	..	..	+	15.4	151	8.8	7.03	
2	60	2/25/36	+++	3.40	+++	++	++	13.3	174	9.9	4.91	Chronic alcoholism for 20 yr.; little food for 4 mo.; symptoms of Korsakoff's syndrome; good recovery
		3/11/36	++	....	++	+	+	11.5	200	8.9	5.61	
		3/24/36	..	4.40	..	..	+	13.1	227	9.2	6.27	
3	32	7/ 7/32	+++	5.00	+++	+++	+++	8.4	...	...	....	Died of pneumonia; necropsy revealed extensive loss of myelin in tracts of cord and peripheral nerves
		7/16/32	+++	....	++	++	+++	7.1	...	...	....	
4	23	3/28/32	+++	4.80	+	..	+++	9.8	...	...	....	Chronic alcoholism; poor appetite; good recovery
5	58	12/ 7/33	+++	1.65	++	..	+++	15.3	125	7.9	....	Subsisted on inadequate diet for preceding 2 yr.; partial recovery
		12/29/33	+	3.00	..	..	+	14.2	198	9.5	6.34	
6	19	5/28/35	+++	2.37	..	+	+++	9.8	123	6.4	5.95	Died of inanition and diarrhea; necropsy revealed extensive loss of myelin in tracts of cord and peripheral nerves
7	30	2/ 1/35	+++	3.14	..	..	+++	14.1	108	7.6	5.49	Chronic alcoholism; had eaten poorly for past 2 or 3 yr.; gradual recovery
		2/ 8/35	+++	....	..	..	+++	11.8	168	8.4	6.27	
		2/18/35	+++	....	..	..	++	13.8	197	10.0	6.22	
		3/ 4/35	++	....	..	..	++	13.0	209	12.0	6.44	
		4/ 4/35	..	4.20	..	..	+	15.0	200	9.8	6.61	
II. Patients with Polyneuritis but no Undernutrition												
8	57	8/28/36	++	4.20	..	+	0	16.32	288	10.1	6.95	Diet of tea and toast for 3 yr.; good recovery
9	35	1/25/35	+++	3.20	..	+	0	18.2	246	12.5	6.20	Course rapidly downward; necropsy revealed striking loss of myelin throughout brain, cord and peripheral nerves
10	48	4/15/32	+++	4.80	..	+	0	13.4	...	....	....	Downward course; necropsy revealed loss of myelin in cord and peripheral nerves
11	46	4/18/35	++	4.00	..	+	Obese	18.3	276	10.6	6.93	Chronic alcoholism; diet of bread and potato; good recovery
		9/29/36	++	....	..	+	Obese	36.1	462	20.0	7.37	Relapse; condition similar to that on first admission; improvement
		10/ 5/36	+	....	..	..	0	28.5	456	17.8	7.11	
		10/13/36	..	4.40	..	..	..	28.4	495	16.5	7.90	
		10/19/36	..	....	..	..	..	26.7	...	15.1	7.53	
III. Patient with no Polyneuritis but with Stomatitis, Anemia and Extreme Undernutrition												
12	39	9/11/33	..	2.85	..	+	+++	8.5	83	5.6	7.13	Had lived on poor diet from 2-3 yr.; no free hydrochloric acid in stomach; good recovery
		9/26/33	..	3.10	..	..	++	11.3	129	7.7	6.74	
		10/ 5/33	..	4.00	..	..	+	13.2	168	10.1	6.98	

When these figures are contrasted with those for the second group of four subjects, in whom there were symptoms of deficiency disease but no undernutrition, a striking difference can be observed. All the values for cholesterol were close to or above the high limit for normal of 250 mg. per hundred cubic centimeters. The total fatty acid content was also well above the median normal value, of 12.5 milliequivalents.

Two of the patients who were not undernourished were treated late and did not recover. Necropsy revealed extensive demyelinization of the peripheral nerves and tracts of the cord similar to that seen post mortem in patients in group I.

The patient in case 12 was included because evidences of lesions of the nervous system were practically absent and the lesions of the skin and anemia were of only moderate severity, while the state of undernutrition was as extreme as that of any of the patients. The extremely low cholesterol and total fatty acid contents of the serum illustrate what may happen when undernutrition is the outstanding factor.

The four patients with undernutrition and polyneuritis, as well as other symptoms of deficiency disease, who were studied repeatedly during recovery, showed a marked rise in lipoids, which was also associated with an increase in weight. The patient in case 12, who had marked undernutrition and little, if any, neuritis, also showed this marked rise in lipoids as recovery progressed.

The patient in case 11 was studied in 1935, during an attack of polyneuritis and symptomatic psychosis, at which time she was obese and the lipoids were high. A year later she returned, weighing more than ever and with similar symptoms. On this admission she was studied repeatedly during the course of recovery. The serum lipoids were high in the beginning and showed little tendency to fall as she recovered from the neuritis.

In the twelve patients studied the degree of anemia did not correspond consistently with the level of the serum lipoids. The total proteins and the serum albumin tended to be diminished when the cholesterol was low.

COMMENT

The aforementioned observations indicate that a deficiency of calories in the food is an important factor in lowering the level of the lipoids in the blood. Furthermore, a diet sufficiently lacking in vitamins B_1 and B_2 (G) and possibly A to produce lesions of the nervous system and the skin does not lower the serum lipoids unless severe undernutrition is also present.

These studies lend no support to the statement of some observers that a rise in serum lipoids may be produced by deficiency in such vitamins as B_1 and B_2 (G) and possibly A.

In spite of the fact that most of the patients in this series were studied in the acute phases of development of the lesions of the nervous system, little evidence of an associated rise in serum lipoids can be discovered. In the patient in case 6, for example, lesions were developing rapidly at the time the serum was studied, and there was no elevation in lipoids. Necropsy, which was performed three days later, showed extensive and recent lesions of the myelin sheaths and nerve cells.

On the other hand, it is possible that the fatty acids may be increased during the acute phases of disintegration of the nervous system but that the changes are masked by the depleting effects of undernutrition. This is suggested by the relatively high amounts of fatty acids found in the initial study of the patients in cases 7 and 2, which fell as the neuritis disappeared and rose again as the state of nutrition improved. The high values for fatty acids found in the polyneuritic patients who were not undernourished also suggest that an increase may occur and that the comparatively low amounts of fatty acids in the markedly underweight patients may have been due to the masking effect of undernutrition. It is noteworthy that, with the exception of the patient in case 11, the cholesterol and phosphatides were not elevated as were the fatty acids during the stage of severe neuritis. In the obese patient in case 11, who was studied repeatedly during recovery from acute polyneuritis, the phosphatides as well as the fatty acids showed a tendency to fall with complete recovery from the neuritis.

SUMMARY

The lipoids of the blood serum of twelve patients presenting severe symptoms of deficiency disease were studied. Seven of the patients had symptoms indicative of marked lesions of the nervous system and severe undernutrition, while four, although suffering from similar lesions of the nervous system, were not undernourished. The patient in case 12 presented few, if any, symptoms of disorder of the nervous system but had cutaneous lesions, anemia and extreme undernutrition. A comparison of these groups gave the following results.

1. The cholesterol and phosphatide contents of the serum were either much below or on the edge of the limits of normal in all the undernourished patients. The values for total fatty acids were low in four patients and close to the median figure for normal in three others.

2. The figures for total fatty acids, cholesterol and phosphatides were either within or above the range of high normal values in the well nourished patients.

3. It was concluded that malnutrition alone accounts adequately for a low lipoid content of the blood in deficiency diseases.

4. No evidence was obtained to indicate that prolonged subsistence on diets sufficiently lacking in vitamins B_1 and B_2 (G) and possibly A to produce changes in the nervous system and, in some instances, lesions of the mouth and skin has an effect on the lipoid content of the blood, except that due to undernutrition.

5. The process of acute demyelinization of the nervous system was accompanied only occasionally by an elevation in the total fatty acid content of the serum and not by a rise in the cholesterol or phosphatide content. In one patient the phosphatides followed the same course as the fatty acids.

REPORT OF CASES

The following patients were treated by supplementing a well balanced diet with such concentrates of vitamins B and G as vitavose or bemax. From 8 to 16 ounces (206 to 453 cc.) of orange juice a day was given when deficiency of vitamin C was suspected. Hypochromic anemia was treated with large amounts of reduced iron.

CASE 1.—A man aged 56, who was admitted on Aug. 10, 1936, had, after his wife's death four years before, begun to drink more and eat less. One month before, he noticed that he had weakness and some dyspnea on exertion and that his feet swelled in the evening. The edema increased until it involved the scrotum. At about the same time he noticed painful swelling of the gums and cheeks.

Examination.—The patient seemed indifferent and sleepy. When aroused, he talked but complained that it hurt his mouth. He was hazy as to recent but clear on past events. He was oriented for place and person but was uncertain about time. The whole inside of the mouth was reddened, injected and somewhat edematous. The inflammation extended into the tissues of the neck. The mucosa of the mouth was dotted here and there with a grayish exudate. Definite pitting edema was found from the lower lumbar region to the feet. There were tremor of the tongue and hands and tenderness over the nerve trunks of the lower extremities.

Laboratory Data.—The blood count was: red cells 3,200,000, hemoglobin content 71 per cent and white cells 11,000. The red cells showed definite achromia and slight anisocytosis. Cultures of material from the mouth revealed chiefly fusiform bacilli and spirochetes.

Course.—The patient responded well to treatment; at the end of four days the edema had practically disappeared. He had recovered when discharged on September 1.

CASE 2.—A man aged 64, who was admitted on Feb. 22, 1936, had, during the preceding four or five years, gradually lost interest in business and increased his consumption of alcohol. For six months he had eaten little food and had become increasingly weak. He had lost at least 25 pounds (11 Kg.) in six months; in the two months prior to admission there had developed swelling of the ankles, black and blue spots on the hands, bleeding of the gums, diarrhea and progressively increasing numbness and tingling of the fingers and toes.

Examination.—The patient was apathetic; memory for recent events was inadequate. Orientation was impaired for time and person. The skin was dry and wrinkled, and there were pigmented areas over the arms, hands and shins. Patchy, ecchymotic areas were present over the dorsa of both hands, chest and shins of

both legs. The tongue was very red; there was atrophy of the papillae around the edges, and the gums were swollen. There was marked tremor of the hands and muscles in other parts of the body, as well as tremor of the tongue and some slurring of speech. The reflexes were all hyperactive, with ankle clonus bilaterally. Bone conduction sense was absent in the ankles and diminished over most of the legs. Generalized weakness of all the muscles of the body was marked. Tenderness was noted over the nerve trunks of both legs.

Laboratory Data.—Analysis of the gastric contents revealed no hydrochloric acid after the administration of alcohol or histamine. The blood count was: red cells 3,400,000, hemoglobin content 75 per cent and white cells 6,800.

Course.—A dilute liver extract[12] was given parenterally every three days, in amounts ranging from 5 to 10 cc. The patient improved rapidly. At the time of discharge, on April 1, the tremor had disappeared, and he had regained strength but still had slight numbness in his hands.

CASE 3.—A woman aged 39 was admitted on June 27, 1932. She had been a chronic addict to the use of alcohol for at least nine years and during the past year had been drinking as much as from 4 to 16 pints (1.8 to 7 liters) of alcohol splits each week. In March 1932 she experienced difficulty in walking and had pains in the legs. Numbness and alternating sensations of heat and cold followed the attacks of pain, and the patient took to bed. She lost appetite and ate little, and her weight decreased rapidly.

Examination.—The patient was emaciated, weighing only 37.19 Kg., whereas one year previously she had weighed 70.4 Kg. At first the skin seemed uniformly sunburned but later became discolored and thickened and exfoliated in sharply demarcated areas over the dorsa of the hands, wrists, face and upper anterior portion of the chest. The gums were edentulous, and the tongue showed a "bald spot" and a bright red, "beefy" margin. White mucous patches were also present throughout the mouth, and there was marked salivation.

The patient was uncooperative and had frequent opisthotonic spasms. Wasting, atrophy and twitching were marked in the facial musculature. Fine and coarse tremors were present in the tongue. All deep reflexes were hyperactive except the achilles, which was absent bilaterally, but the patient had marked foot drop, with shortening of the cords of both heels. There were marked weakness in extension of both hands and a bilateral main en griffe; spastic quadriplegia was present, but the legs were more involved than the arms. Superficial and deep sensation was diminished over the entire body.

The patient was confused and showed much random spontaneous activity of the extremities; some purposeful motor activity, however, could be elicited. Numerous spells of laughing and crying occurred. She spoke spontaneously and occasionally in response to questions, but speech was usually rambling and incoherent. She had delusional ideas and hallucinations. Orientation and memory were impaired.

Laboratory Data.—Examination of the cerebrospinal fluid revealed: xanthochromia; a negative Wassermann reaction and a colloidal benzoin curve of 0024443222.

Course.—Three days after admission diarrhea and retention of urine developed. The patient was catheterized on several occasions, and severe cystitis appeared; an inlying catheter was inserted, and the amount of pus in the urine diminished. She was fed with a tube and given the vitamin B concentrate of Block and Cow-

12. Solution liver extract-Lilly (N. N. R.) was used.

gill.[13] In addition, clyses of dextrose and saline solution were administered. The appetite improved markedly. Soon after, however, pneumonia developed, and the patient died, on July 25.

Necropsy.—The cortical nerve cells showed axonal changes, which were present to the most marked degree in the giant cells of the motor cortex but were also observed in nuclei of the cerebellum and cord. The spinal cord disclosed striking lesions in preparations stained by nearly all histologic methods. Marchi preparations revealed that the funiculi gracilis and cuneatus were completely destroyed on both sides. By no means did destruction of the medullary sheaths confine itself to the posterior columns, for, although less extensive, it was present in nearly every other fiber tract of the spinal cord. Extensive destruction of the medullary sheaths was seen in all the peripheral nerves studied.

Case 4.—A white woman aged 23, married, who was admitted on March 26, 1932, for many months had consumed as much as a quart (946 cc.) of gin daily and had eaten little more than bread and coffee. In May 1931 the patient suffered a spell of confusion and "paralysis" of the legs. The confusion cleared, but weakness of the legs became worse, so that it became necessary for her to grasp nearby objects for support in walking. The physical condition became progressively worse, but the patient remained completely oriented and was apparently rational. On Jan. 1, 1932, she suddenly became confused and "talked queer things;" subsequently she had convulsions.

Examination.—The patient was agitated and expressed many delusions; she muttered unintelligibly and had hallucinations. Frequently she cried bitterly as if in the presence of something which frightened her terribly. On one occasion she mentioned that animals were about her. Generally she was apathetic, and she smiled only rarely. Her weight was 40.82 Kg.; she was emaciated, and the musculature of the arms and legs showed atrophic changes. The legs were held constantly in a position of semiflexion and were spastic. She complained of pains in the legs and the soles of the feet. There were fine tremor of the lower part of the face and fine and coarse tremors of the tongue. All deep reflexes were extremely hyperactive, and a well sustained ankle clonus was elicited bilaterally. The abdominal reflexes were absent, and there was incontinence. The patient could stand, but there was little strength in the arms and legs. There was fibrillary twitching of the musculature of the face, arms and hands. Coordination was profoundly disturbed in the arms but could not be tested in the legs because of the spasticity. There was inconstant dysarthria. The proprioceptive sense was diminished in both legs.

Laboratory Data.—Examination of the spinal fluid revealed an initial pressure of 75 mm. and a Pandy reaction of 2 plus.

Course.—Disorientation soon disappeared, as did the delusions and hallucinations. Memory for recent events was recovered slowly, and all sensory disorders cleared. The left leg became completely relaxed, mobile and free from pain; recovery of the right leg was considerable, although some flexion deformity and pain persisted. The weight rose to 46.7 Kg. at the time of discharge, on June 7.

Case 5.—A man aged 56, an Irish American, was admitted on Dec. 2, 1933. His wife during the three or four years prior to his admission had become increas-

13. Block, R. J.; Cowgill, G. R., and Klotz, B. H.: Antineuritic Vitamin: Method of Assay, Concentration of Vitamin with Silver Under Various Conditions, and Its Solubility in Certain Organic Solvents, J. Biol. Chem. **94**:765, 1932. Block, R. J., and Cowgill, G. R.: Antineuritic Vitamin: Removal of Impurities by Oxidizing Agents, ibid. **96**:127, 1932.

ingly peculiar and difficult, and the patient found it hard to make enough money to support her whims. He received little to eat. He had vague gastric complaints and constipation. Several physicians told him that he had an ulcer of the stomach, and a Sippy diet was prescribed. He accepted most of the prohibitions of the Sippy regimen and took only the powders and skimmed milk, supplemented with bread and potato. During two years on this pseudo-Sippy diet he lost weight and strength. Eight weeks before admission severe pain developed in the lower extremities. The pain was sharp and radiated down the thighs of both legs. Then the feet and ankles began to swell, and a bluish swelling spread over the thighs and down the calves of the legs. At about the same time he practically gave up eating. Diarrhea began three or four days before admission.

Examination.—The patient was poorly developed, ill nourished and dehydrated, with brownish, scaling pigmentation over the backs of the hands and on the anterior surfaces of the lower parts of the legs. The mouth was edentulous; the tongue was thick and reddened, and there were numerous ecchymotic spots in the throat. Both knees were swollen and hot and showed deep blue discoloration in spots, which faded into various shades of green and yellow. There were weakness of all the muscles and diminished vibration sense over the lower extremities.

Laboratory Data.—Examination of the urine showed a reaction of 1 plus for albumin and numerous clumps of white cells. The blood count was: red cells 1,650,000, hemoglobin content 32 per cent and white cells 8,400; the smear showed achromia and marked differences in the size and shape of the red cells. Roentgen examination of the gastro-intestinal tract revealed no evidence of gastric ulcer.

Course.—By December 9 the red cell count was 3,050,000, and the hemoglobin content, 40 per cent; the reticulocytes had risen to 22.4 per cent. After this the reticulocytes diminished slowly. By January the red cell count was over 3,000,000, and the hemoglobin content was approximately 70 per cent. On discharge, at the end of December, the patient was able to walk about and was moderately strong.

Case 6.—A Jewish lad aged 18, who obviously was critically ill, was admitted on May 23, 1935, in an emaciated and semistuporous condition. He had always presented a feeding problem. At the age of 11 years he complained that he had terrible abdominal pain. No diagnosis was made. This was followed by chronic diarrhea, varying from three to twelve stools a day. He would recover for two or three months after being in a hospital, but on his return home the diarrhea would appear again in a month or so. At the age of 14 there developed an ischiorectal abscess, which was operated on at the New Haven Hospital. After the age of 15 the course was gradually down-hill, with remissions and exacerbations. Examination in different clinics failed to reveal the specific source of the chronic enterocolitis and the fistula in ano.

Examination.—There were marked emaciation and chorea; the patient weighed 32 Kg. Pigmented areas, with some scaling, were observed over the dorsa of the hands and arms and the nose. The tongue was red, with slight atrophy of the papillae. A deep fistula in ano discharged pus. The testes were atrophic. The patient was apathetic and disoriented for time and person. It was difficult to determine whether his memory was impaired or whether he was too apathetic to make the effort to answer questions. Marked muscular wasting was evident throughout the body. The patient tended to assume a position in which his arms and legs were flexed. The knee and ankle jerks and arm reflexes were markedly hyperactive. Bone conduction in the lower extremities was impaired.

Laboratory Data.—The blood count was: red cells 2,000,000, hemoglobin content 26 per cent and white cells 3,000; a smear showed marked variability in the size

and shape of the red cells and in their staining qualities. The calcium content of the serum was 8.5 mg. per hundred cubic centimeters, and the phosphorus content, 4.22 mg.

Course.—Shortly after admission tonic convulsions developed, and on the basis of the low calcium content, the patient was given calcium gluconate intravenously, without much change in his condition. Transfusions on two occasions helped only temporarily. The patient died on May 31.

Necropsy.—Chronic ulcerative enterocolitis and appendicitis, with multiple fistulas, fibrous adhesions in the peritoneum, a fistula in ano, splenomegalia and hepatomegaly were observed. Practically no subcutaneous fat was present anywhere in the body. The nervous system displayed marked demyelinization of the tracts of the spinal cord and the peripheral nerves; axonal degeneration of the Betz cells of the motor cortex was noted. There were also marked atrophy of the skin, scaling of the skin of the face and marked chronic glossitis.

CASE 7.—A white woman aged 43, of American-English stock, who was admitted on Jan. 29, 1935, after marriage at the age of 20 had become a social butterfly and spent most of her time at bridge parties and in drinking. Indulgence in alcohol had increased, until by 1930 she was eating little and was drunk a great deal of the time. In May 1934 there were pains in the legs. She had lost a great deal of weight and was hospitalized; later she recovered. In August 1934 she again began to drink and not to eat. By December she was vomiting frequently in the morning and taking alcoholic "pick me ups." In January 1935 she had a chill and slight fever, which were succeeded by a state of mental confusion and hallucinations.

Examination.—The patient was critically ill and markedly dehydrated and undernourished and had a temperature of 104 F., with a pulse rate of 120 and a respiratory rate of 28. The right pupil was irregular, and there was definite lateral nystagmus. There were marked tremor of the hands and tongue and general unsteadiness of the whole body when she attempted to sit up. A mild degree of primary atrophy of the optic nerves, weakness of the legs, spasticity and absence of vibratory sense below the knees were observed. Position sense in the lower parts of the legs was also impaired. Ankle and knee jerks were obtained only on reenforcement. The patient was much disturbed by persecutory delusions and auditory hallucinations. She was oriented as to place but was uncertain about persons and time.

Laboratory Data.—The blood count was: red cells 3,140,000, hemoglobin content 70 per cent and white cells, 6,500. There was considerable variation in the size and shape of the red cells, and a few macrocytes were observed. Examination of a catheterized specimen of urine showed numerous white cells and albumin. Analysis of the gastric contents revealed that free hydrochloric acid was present only after the administration of histamine.

Course.—During the first three days the patient received parenteral injections of physiologic solution of sodium chloride and dextrose. For the first week paraldehyde was used as a sedative. A dilute liver extract, 2 cc., was given daily for two weeks. Symptomatically she made a much better recovery than was shown by the rise in the red cell count, which at the time of discharge, on April 8, was 4,200,000, with a hemoglobin content of 85 per cent. The return of bone conduction sense was partial, but other symptoms had disappeared.

CASE 8.—A woman aged 57, who was admitted on Aug. 24, 1936, had lived alone with her husband for the past ten years. The business depression left them

short of money, and they did not go out at all. For three years preceding admission her food consisted practically entirely of toast, tea and potato. She had lost weight but was still obese.

Examination.—The patient, a stocky woman with a double chin, was apathetic and too weak to walk. The hair was coarse; the eyebrows were thin, and there were some scaling and slight pigmentation of the dorsa of the hands. The tongue was smooth, with some atrophy of the papillae. Pressure over the nerve trunks of all extremities elicited the complaint of pain, and there was also superficial tenderness of the skin. A tourniquet test of the arms produced numerous pinpoint petechiae.

Laboratory Data.—The blood count was: red cells, 4,200,000, white cells 5,240, and hemoglobin content 76 per cent; a smear revealed nothing remarkable. The basal metabolic rate was —13 per cent. Chemical analysis of the blood serum revealed: calcium 10.03 mg. per hundred cubic centimeters, phosphorus 3.5 mg. and nonprotein nitrogen 34 mg.

Course.—Persuasion and feeding with a spoon were necessary to induce the patient to take 1,000 calories during the first four days. During the first week cevitamic acid, 0.1 Gm. in 50 cc. of saline solution, was injected intravenously. A tourniquet test gave negative results at the end of this week. On discharge, against advice, on September 6, the patient was up and about and was much stronger and more talkative. Pains in the arms and legs had practically disappeared. The red cell count had risen to 5,000,000; the hemoglobin content was 86 per cent, and the white cell count, 7,400.

CASE 9.—A white woman aged 35, who was admitted on Jan. 20, 1935, had been a heavy drinker for at least five or six years. After her husband had been committed one year ago to an institution for treatment of delirium tremens, the patient began to drink more. A social worker reported that eight months previously the patient was on the verge of delirium tremens but that, on threat of being taken to jail, she sobered up for a short time. Six weeks before admission she complained of numbness and tingling of the hands and feet; then her legs became so weak that she was unable to walk. This was followed by vomiting, which lasted for six or eight days. The hallucinations and "funny" movements of her arms were said to have been present for at least eight or nine days.

Examination.—The patient was lying in bed, looking up at the ceiling with an anxious expression on her face. She talked chiefly of the pains in her legs and of hallucinations which caused her much fear. She said she saw animals and people. She was disoriented for time and place, and there was loss of memory for recent events, with confabulation. She was well nourished. The neurologic findings consisted of peripheral neuritis involving the arms and legs and disorders consisting of extrapyramidal origin, choreiform and athetoid movements.

Laboratory Data.—The blood count was: red cells 3,200,000, hemoglobin content 80 per cent and white cells 8,000. Examination of the urine showed a trace of albumin and a constantly positive reaction for urobilin.

Course.—The patient was given daily 3 cc. of concentrated liver extract[14] by parenteral injection, as well as feedings with a spoon. She seemed to be improving, when pneumonia developed on February 4. She died on February 6.

Necropsy.—Two processes were observed in the nervous system. One was encephalitis haemorrhagica superior of the Wernicke type. In the maxillary

14. Solution liver extract concentrated-Lilly (N. N. R) was used.

bodies were marked vascular fibroblastic and glial proliferative reactions. The other process consisted of diffuse, severe degeneration of the medullary sheaths of the peripheral nerves. There was also demyelinization of the posterior columns of the spinal cord. The ventrolateral nuclei in the lumbar region of the spinal cord showed many nerve cells with axonal changes. Nissl preparations of the motor cortex showed that the Betz cells were almost without exception the seat of marked axonal changes. The changes observed were identical with those noted in persons with chronic alcoholism who have a pellagroid syndrome.

CASE 10.—A man aged 48, a Lithuanian, who was admitted on April 11, 1931, had been in bed with "pneumonia" five years previously; after this he began to drink a great deal. He became "nervous" and irritable and frequently had no appetite. Sixteen months before there developed generalized weakness and tremor, accompanied by headache, loss of appetite, nausea, vomiting and dizziness. These symptoms lasted about a week, but he did not entirely recover. Exacerbations and remissions of the symptoms occurred. He had no appetite and ate only bread and potatoes. Two weeks before admission he began to "wander in his speech," laugh in a silly fashion and say that he saw "babies walking with men" on the wall.

Examination.—The patient was uncooperative, mumbled to himself and was disoriented; often he tried to get out of bed but was usually too weak even to sit up. It was always impossible for him to stand. The tongue was red and slightly swollen. Some scaling of the skin was present over the hands and feet, but there was no definite increase in pigmentation. There were marked weakness and slight atrophy, as well as some spasticity, of the left arm and of both legs. Deep and superficial reflexes were present, but were much more active on the left than on the right. There were sustained ankle clonus bilaterally and hyperesthesia to superficial and deep pressure over the left arm and leg. Vibratory sense could not be tested.

Laboratory Data.—Laboratory examinations revealed nothing remarkable.

Course.—The patient was difficult to nurse and to feed. He died of pneumonia two weeks after admission.

Necropsy.—The nerve cells of the cortex showed distinct changes in Nissl preparations. In the giant cells of Betz and the motor cells of the anterior horns of the spinal cord the cytoplasm had a hyaline appearance, and nuclear eccentricity was marked. The appearance of these cells was identical with that in the axon reaction. Many of the cortical nerve cells contained large quantities of lipoid material.

The most striking changes were those in the spinal cord. In addition to the axonal changes in the cells of the anterior horns, stains for medullary sheaths revealed areas of degeneration scattered through the pyramidal and sensory tracts.

CASE 11.—A white woman aged 46, of Irish-American stock, who was admitted on March 25, 1935, about ten years before had begun to drink more than formerly. Indulgence increased, until during the two years prior to admission she was drunk almost every night. For the preceding year and a half she had eaten very little meat or green vegetables. In March 1934 she complained of pins and needles in her feet and weakness and difficulty in walking. During February 1935 she drank progressively more and found it difficult to sleep. On March 23 she was stuporous most of the day. It became difficult to rouse her and she was sent to the hospital.

Examination.—The patient was stuporous for the first twenty-four hours but could be roused during this period, particularly by pressure over the nerve trunks of the arms and legs. She was obese, her weight being 95 Kg.; the tongue was

coarsely tremulous, and the deep reflexes of the lower extremities were absent. When she recovered from the stuporous state, at the end of about forty-eight hours, she became irritable and restless. It was necessary to use continuous baths for sedation. She was also given paraldehyde at night. She was disoriented for time and occasionally for place and person. She was also suspicious of every one; she thought that the food was poisoned, and it was difficult to get her to eat.

Touch and pain sense were normal; position sense was good; vibratory sense was diminished from the waist down. On the left side vibration sense was absent over the ankle and shin. The ankle and knee jerks were absent. The tongue was thick and red, but there was no atrophy of the papillae.

Laboratory Data.—The blood count revealed: red cells 4,000,000, hemoglobin content 90 per cent and white cells 7,200. Approximately 300 mg. of bromides per hundred cubic centimeters of blood was found.

Course.—On discharge, against advice, on April 18, the patient was not entirely well. The knee and ankle jerks were still absent, but the sensory disturbances had practically disappeared. There was still diminished vibration sense in the lower parts of the legs.

Intervening History.—The patient adjusted well at home, and it was only after her husband's death, on Sept. 18, 1936, that she resumed drinking in tremendous quantities. She vomited frequently and ate very little.

Second Admission.—When readmitted on Sept. 27, 1936, the patient was drowsy and disoriented for place and person. She was more obese than before, her weight being 100 Kg. Her mood was depressed. There was tenderness over the nerve trunks of both legs. The knee and ankle jerks were absent. Vibration sense was diminished over the patella and absent at the ankles. Other sensory modalities were not remarkable. Some atrophy of the papillae of the tongue was present.

Course.—Liver extract, 2 cc. intramuscularly, was given each day for the first five days. By the end of a week the patient's mental condition had cleared, except that she was still rather tearful over the loss of her husband and her future plans. Tenderness over the nerve trunks disappeared, but the vibration sense did not return. By October 3 she was up and about the wards but remained somewhat depressed and suspicious of the physicians. She was still under hospital care on October 28.

CASE 12.—A mulatto woman aged 39, who was admitted on Sept. 9, 1933, had had very little money for food. For four years she had lived on beans and bread, with meat only once or twice a month; during that time her weight decreased from 51 to 43.5 Kg. During these years metrorrhagia and general weakness were the marked symptoms. One and a half years ago she became progressively weaker, and there developed shortness of breath and swelling of the ankles in the evening.

Examination.—The patient was pale; shortness of breath was evident on slight exertion. She was undernourished, and the skin was wrinkled. The papillae about the edges of the tongue were atrophied. General weakness of all the muscles of the body and slight edema of the ankles were observed.

Laboratory Data.—The blood count was: red cells 2,850,000, hemoglobin content 28 per cent and white cells 7,000; the differential count was not remarkable. In the smear the red cells showed marked achromia and some anisocytosis; the reticulocyte count was 2.8 per cent.

Course.—The patient improved on dietary treatment. Normal menstrual flow returned. At the time of discharge, on October 6, she had recovered a good deal of strength and 2.5 Kg. in weight; the red cell count was 4,000,000, with a hemoglobin content of 65 per cent.

CEREBRAL DYSRHYTHMIAS OF EPILEPSY

MEASURES FOR THEIR CONTROL

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Our reports on the electrical activity of the brain in epilepsy have thus far been almost entirely descriptive.[1] Interpretation, we believed, could wait until a considerable body of data had been acquired. Now, after two and one-half years, we have electro-encephalograms for over four hundred patients. We have daily records for some patients extending over many days; others have been studied repeatedly at long intervals, and for others we have made long-continued records, the longest being thirty-four hours. Altogether, we have a total of approximately 60 miles (96 kilometers) of records. Most of these records were made with a multichannel instrument recording simultaneously from four parts of the head.

The object of this effort has been to secure electro-encephalograms of patients during seizures, but we also wished to see what abnormalities, if any, occurred in the interval between seizures. We have records of the grand mal seizures of thirty patients—a total of fifty grand mal seizures. We have records of psychomotor attacks in six patients—a

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1. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133 (Dec.) 1935. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: The Electro-Encephalogram in Diagnosis and in Localization of Epileptic Seizures, ibid. **36**:1225 (Dec.) 1936. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: Effect on the Electro-Encephalogram of Drugs and Conditions Which Influence Seizures, ibid. **36**:1236 (Dec.) 1936. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: The Effect on the Human Electro-Encephalogram of Certain Drugs Which Influence Nervous Activity, Arch. Int. Med. **60**:158 (July) 1937; Epilepsy, a Paroxysmal Cerebral Dysrhythmia, Brain, to be published.

total of fifteen psychomotor attacks. We have records of the petit mal seizures of seventy-six patients and of many thousands of individual attacks of the petit mal type. We have studied various patients, asleep and awake, with sedatives and without, after the administration of stimulants and small doses of convulsants, during induced anoxemia, hyperglycemia and hypoglycemia and during shifts in the acid-base equilibrium of the blood. We have not investigated sufficiently the effects of alterations of water balance. This, and much more, remains to be done. In view, however, of the volume of the data accumulated, and what is more important, of the clear pattern into which the observations arrange themselves, we believe that interpretation is now warranted.

WHAT IS EPILEPSY?

To many, the existence at present of any satisfactory answer to this question may seem altogether unlikely, and the answer which we shall give may seem preposterous. Electro-encephalography has developed so rapidly that it is not surprising to find that competent neurologists and physiologists react to data from this source with astonishment and incredulity. However, careful consideration will, we believe, convince even the most incredulous that our electro-encephalographic data are in agreement with significant data derived from clinical and laboratory sources.

Our answer, then, to the question "What is epilepsy?" is: "Epilepsy is disordered functioning of the rate-regulating mechanisms of the brain." It is a paroxysmal cerebral dysrhythmia. Our evidence for this statement is as follows: Grand mal epilepsy is characterized by extreme acceleration of the electrical activity of the cortex; psychomotor attacks, by extreme slowing of this activity, and petit mal, by alternation of fast and slow activity. With these disorders of frequency there are also associated abnormally high amplitudes.

In previous communications we have presented records of the electrical disturbance of the brain during grand mal and petit mal seizures, but have emphasized the latter, since petit mal seizures are the easier to record. We have pointed out that petit mal disturbances are characterized by a wave and spike of large voltage repeated three times a second but that there are individual differences in the wave pattern of individual patients.

With the accumulation of records of other types of seizures, we have found that grand mal types of activity, though characterized by fast waves of high voltage, present a good deal of individuality in individual patients. The grand mal type of activity is unmistakable, and if the patient is having a convulsion, the dysrhythmia is present in records

taken from all points of the accessible cortex. The same type of arrhythmia (though shorter in duration and of less voltage) may also be present in patients subject to grand mal at times when they present little or no evidence of seizure. The grand mal activity encountered in six patients is shown in figure 1. In all but one of these patients the abnormality came and went without convulsive manifestations. The abnormalities appeared spontaneously, save in the fifth patient, F. L., in whom these series of spikes followed the subcutaneous injection of insulin. In the records of R. O. and R. P. a few square-topped waves of the psychomotor type are interspersed among the spikes.

Since our last communication in the ARCHIVES, we have observed a third type of electrical activity, distinct from those of petit mal and

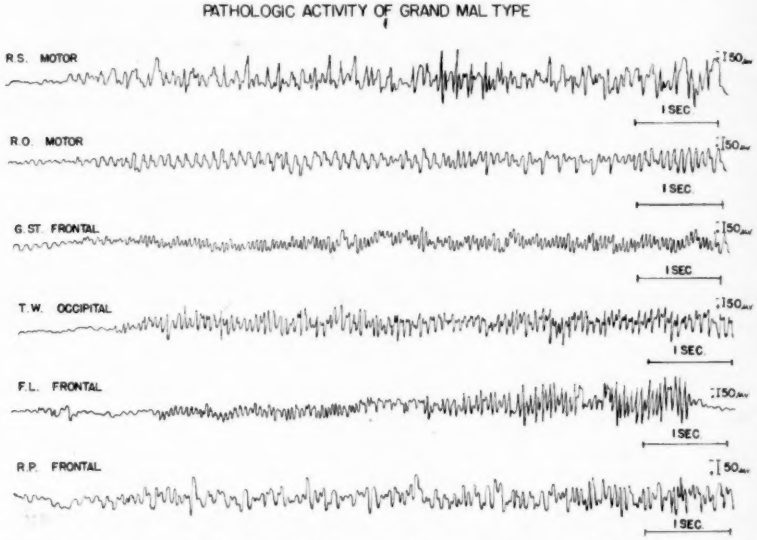

Fig. 1.—Electro-encephalographic records of six patients, showing pathologic activity of the grand mal type. In each record the patient's initials and the portion of the scalp to which the "active" electrode was attached are indicated at the left. At the extreme left of each tracing is a short portion showing the patient's normal activity. In this figure and in several subsequent figures, the time scale for one second and the signal made by 50 microvolts appear at the right. The "indifferent" electrode, which was ordinarily connected to "ground" on the amplifier, was attached to the lobe of one or both ears.

grand mal, which occurs in seizures ordinarily classed as psychic variants, or equivalents. In these attacks the patient, though he may perform apparently conscious acts, is not subject to command; he may exhibit involuntary tonic movements; he may display psychomotor disturbances of a surly, unpleasant sort, and on recovery he has complete amnesia for the events which occurred in the attack.

These interesting, but disconcerting, psychic episodes accompany cortical action potentials which are of high voltage and slow frequency —from 3 to 6 a second. There are series of regular, square-topped waves with the normal rhythm of from 8 to 10 a second still present on the crest. The appearance is that of a positive potential which recurs at the rate of from 3 to 6 a second on an otherwise normal rhythm. At another period of the seizure the waves, though still of high voltage, are more irregular and without the crenated crests. In the twilight mental state or on recovery there are wide, slow swings of potential, with preponderance of the normal rhythm. The various stages of a psychomotor seizure which occurred in one of our patients are shown in figure 2. The associated clinical events are indicated in the legend.

This type of dysrhythmia, like the two previously described, may last for several seconds without simultaneous clinical manifestations. Figure 3 is made of samples of the records of eighteen patients who exhibited electrical disturbances of the amnesia or psychomotor type. While these records were being made, the patients appeared normal. The seizures are therefore "subclinical," but the abnormalities differ from those recorded in clinical psychomotor seizures only in their short duration.

In addition to these three types of arrhythmia which can be identified with the three well recognized clinical types of seizures, many patients, when they are without symptoms, show slow (from 2 to 7 a second) waves of large voltage, without spikes and without square tops. Whether these are distinctive for persons with present or prospective epilepsy will require further observations of normal persons and of patients with nervous or mental disorders which are nonepileptic in their clinical manifestations.

Before we proceed further, it would be well to discuss briefly the general nature of the electrical activity of the brain. Electro-encephalography has shown that the brain is the seat of constant rhythmic activity—activity which is altogether similar to that shown by other nerve structures with which all are familiar, for example, the respiratory center and the pacemaker node of the heart.

With what physiologic function is this spontaneous rhythmic activity associated? It is associated with changes in the irritability of the center from which it is obtained. In one phase of the potential fluctuation nerve action potentials tend to be released, and in another, to be held back. If the nerve impulses are released in a tract of nerve fibers which goes to another center, the amplitude and rhythm of the second center are altered, much as the amplitude and rhythm of the heart beat or of respiration are affected by afferent stimulation. In general, the electrical

rhythm of the normal cortex is affected by the same agents and in the same way as the respiratory rhythm. This similarity between the cortex and the respiratory center should not surprise one, for they are formed of essentially similar tissue.

When one compares the types of abnormality which occur in the electrical activity of the cortex in epilepsy with those which are common in the respiratory center, one sees that not only the normal but the abnormal activities of the cortex and the respiratory center are similar. The course of a severe grand mal seizure, as recorded in the electro-

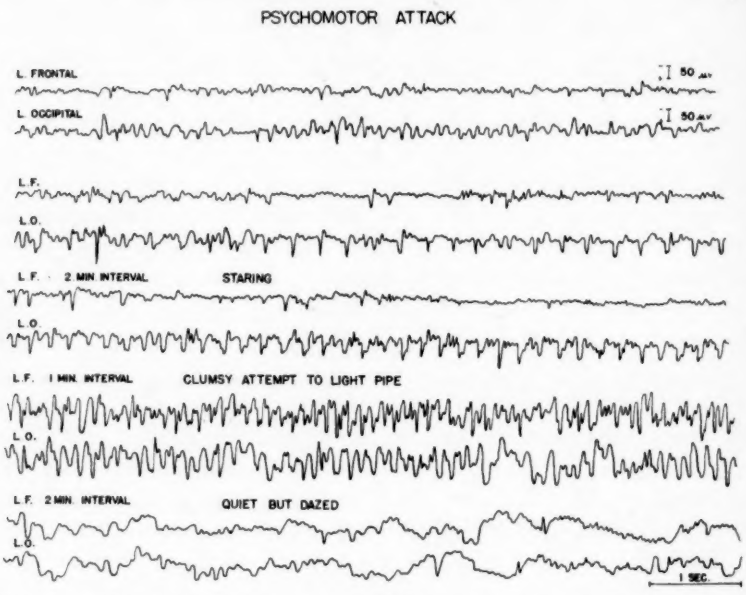

Fig. 2.—Sections from the electro-encephalogram of patient P. H. before, during and after psychomotor seizure. The curves represent two simultaneous tracings of activity, one led off from the left frontal and the other from the left occipital region. The topmost pair of curves represents the patient's "normal" record, made a number of minutes before the seizure began. However, the occipital tracing contains several square-topped waves, which are absent from the records of normal persons. The second pair of tracings, made several minutes later, has square-topped waves, which appear occasionally in the frontal lead and almost continuously in the occipital. At this time the patient was sitting quietly with the eyes closed, apparently conscious. The third pair of records, made two minutes later, shows more and deeper downward (positive) spikes in the occipital lead. The patient had opened his eyes and made no response to the request that he close them. One minute later (fourth pair of curves) he made clumsy efforts to light his pipe, spoke incoherently, tried to leave his chair and finally pulled the electrodes from his scalp. During this period the waves were of higher voltage and faster rhythm. In the lowest pair of records the patient obeyed commands and was quiet but was still dazed. A few minutes later he was again in his usual state, but had no recollection of his seizure and did not know that he had had one.

encephalogram, is compared in figure 4 with the changes in respiratory movements which occur in asphyxia; as will be seen from inspection of this figure, the parallelism, when the time scale is disregarded, is perfect. The changes in cortical potential which occur in petit mal are comparable, if one disregards the time scale, to those for respiratory movements in respiration of the Cheyne-Stokes type (fig. 5), and the slow activity of psychomotor attacks closely resembles slow, gasping respiration.

In less severe seizures the shift in cortical rhythm is from normal to fast and back to normal again, as is true also of the respiratory

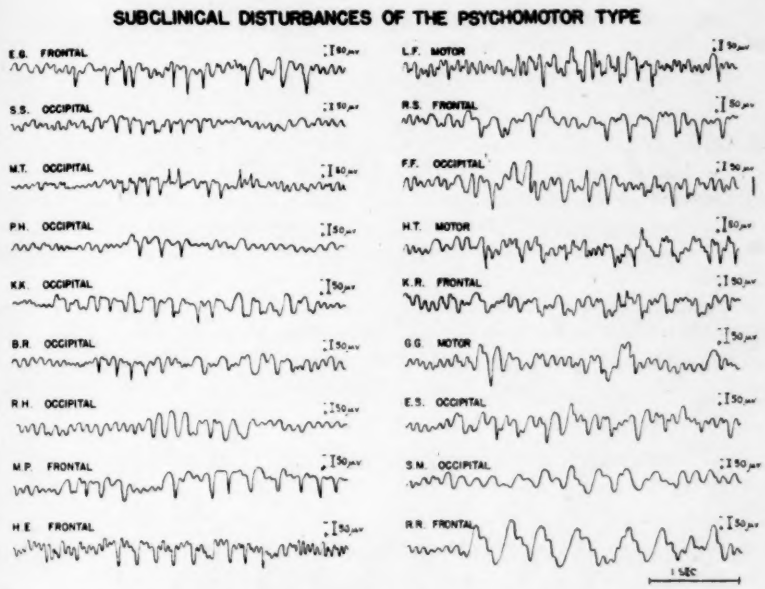

Fig. 3.—The electro-encephalographic records of eighteen patients showing pathologic activity of the "epileptic equivalent," or psychomotor, type. The labels, time and voltage markings have the same significance as those in figure 1.

rate in mild asphyxia. When brain cells are injured, they may die; they may remain "sick," or they may recover entirely. If they die or recover entirely there is no epilepsy, but if they remain "sick" there is epilepsy or, at least, the ground in which epilepsy may develop; for although the cells may not be abnormal enough to produce distortion of electrical frequency and amplitude, a further slight injury, such as even normal stimulation, which is in the nature of slight injury, will cause the "sick" cells to show symptoms. The only symptoms which a nerve cell can show are disorders in regulation of rate.

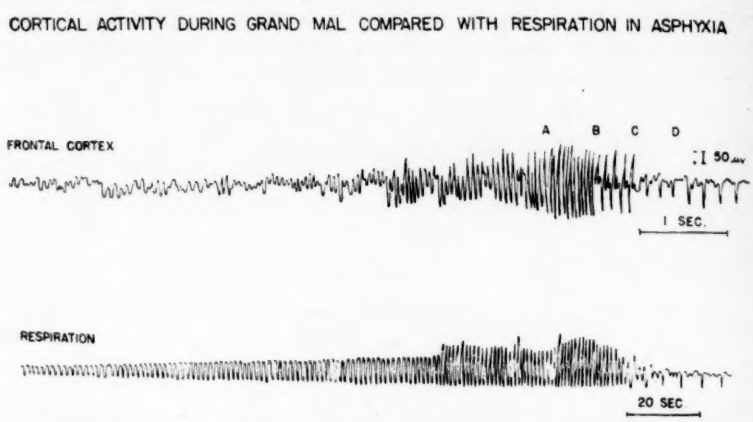

Fig. 4.—Comparison of the activity of the frontal cortex during a grand mal seizure in an epileptic patient with the activity of the respiratory center during asphyxia in a cat. The activity of the frontal cortex was recorded by leading from the lobe of the ear to the ground and from the forehead to the grid of a condenser-coupled vacuum tube amplifier, with the output terminals connected to an ink-writing oscillograph. The activity of the respiratory center is recorded in terms of pressure changes in the trachea. The response was uncomplicated by anesthesia.

It should be noted that the similarity of response in these two cases does not indicate identity of the primary stimuli, for neither of the records is specific for any special stimulus; they are general records of extreme stimulation overcome by depression.

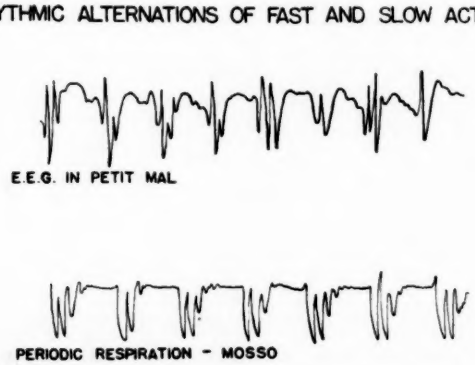

Fig. 5.—Abnormal rhythmic activity of the cortex in one of our patients during a petit mal seizure, compared with the activity of the respiratory center in periodic respiration, copied from an illustration by Mosso. In both cases the mildest form of disordered regulation of rate is represented, for, instead of holding a given rate, the mechanism "hunts" back and forth on either side of the normal rate. More extreme disorganization in regulation of rate results in less rapid adjustment, in slower "hunting" and, finally, in such slow, extreme shifts of amplitude and frequency as hardly to be recognizable as "hunting."

The same basic disorder that underlies epilepsy is observable in an injured peripheral nerve; for in a nerve spontaneous discharges may develop and become synchronized in a number of fibers so as to result in potentials of abnormal amplitude. Such an injured nerve may remain quiet until it is stimulated and thereon respond with a rhythm which is abnormal in both frequency and amplitude. This, then, is "epilepsy" in a peripheral nerve. Limitation of epilepsy to dysrhythmia of the higher centers is therefore an arbitrary and not a logical limitation.

It would probably be well at this time, in view of the emphasis that has been placed by some on the etiologic connections between cerebral anoxemia and epilepsy, to point out that the similarity between grand mal seizures and asphyxia is not to be explained by the assumption that in grand mal the cortex is being asphyxiated. Although the respiratory center gives a response to asphyxia, as is shown in figure 4, this is due not to lack of oxygen in the respiratory center but to the direct stimulating effect of carbon dioxide and indirect stimulation from the carotid sinus. The center in the cord responsible for the scratch reflex might have been chosen instead of the respiratory center for comparison with the cortex. The parallelism, however, would not have been so perfect, for the scratch center does not show spontaneous rhythmic activity. Nevertheless, in the center for the scratch reflex, as in the respiratory center, increasingly strong stimulation results in a series of rhythmic discharges similar to those which occur in a grand mal seizure. In this case the acceleration is unquestionably not due to anemia. The primary disturbance in rate is due to stimulation. Similar words of caution are directed to those who are inclined to believe that the abnormal activity of petit mal is due to anemia. The problem of what causes the cerebral dysrhythmias of epilepsy will be dealt with in a later section of this report.

We have spoken of rhythmic muscular movements as though they were indicators of rhythmic processes in the central nervous system, and so they are. For years physiologists have been using muscle to record nerve potentials and nerve-muscle preparations to record activity of the central nervous system. It is obvious, however, that muscle is at times an inadequate recorder, as for example, when the central activity is exceedingly fast, as is the case in the first part of a grand mal seizure. The muscle responds to this exceedingly fast activity with a single tonic contraction. As slower waves appear in the electrical record, clonic movements synchronous with the electrical waves appear, and as the cortical waves become slower, these movements become slower. Here is the proof of Hughlings Jackson's statement that rigidity, or tonic spasm, is clonus "run together." In petit mal epilepsy blinks of the

eyelids or twitches of a limb tend to correlate with the 3 a second rhythm. As might be supposed, however, there are large areas of the brain where great abnormalities of frequency and amplitude may develop without any accompanying muscular movements.

WHERE DO EPILEPTIC SEIZURES ORIGINATE?

As indicated in the preceding discussion, a disturbance which is essentially epileptic in nature—one which involves rhythmic activity of abnormal frequency and amplitude—may start in any portion of the nervous system. If we follow clinical convention, however, we shall refer only to the dysrhythmias which are of cerebral origin as epileptic. Clinical observations on epilepsy show that seizures consist of a great variety of sensory and motor manifestations, appearing in an almost infinite variety of sequences. Such manifestations of themselves demonstrate sufficiently that there is no portion of the brain which is exclusively involved, nor is it probable that there is a single locus from which seizures always originate. We have seen cases in which there was localized dysrhythmia in one frontal lobe, in both frontal lobes independently, in one motor area or in one occipital lobe. We have found such disturbances more often in the frontal area than in other regions. In many cases abnormal activity appears to start in one area and to spread to the rest of the cortex. In some cases the activity appears to start all over the cortex at once; this suggests strongly that the disturbance comes from a subcortical center.

One of our patients (T. T.) had a record of particular interest.

The boy is now 18 years old; at the age of 2 years he had a convulsion; at 6, after an automobile accident in which his hip was dislocated but his head apparently was not injured, he began to have night terrors and to start violently, sometimes falling to the ground, when frightened by a sudden noise or disagreeable sight. He came under our medical care six years ago, when nocturnal convulsions commenced. In recent months psychomotor outbursts began. At the time of our first electrical studies he was having grand mal seizures daily, and, in addition, myoclonic jerkings frequently and psychic outbursts weekly. Roentgen films showed the presence of small bony exostoses in both frontal regions. Electro-encephalography showed localized activity of the petit mal type in both frontal areas. This was present only during sleep. Injection of phenobarbital, when it produced sleep, also caused the pathologic activity and, in addition, precipitated violent psychic outbursts, which necessitated the use of restraints. Because the abnormal rhythms were confined to the frontal area, we advised that the offending frontal lobes be removed. Dr. Stanley Cobb concurred, and Dr. Jason Mixter performed lobectomy in two stages; at the first operation the anterior third of the frontal lobe was removed, and at the second, about four weeks later, a similar portion of the left frontal lobe was excised. The portions removed were atrophic.

The effect of these operations on the frequency of seizures and on the amount of pathologic activity are shown in figure 6. The parents have been delighted

with their son's improvement. His condition previous to operation had made necessary confinement in a hospital for mental disease. He now displays more intellectual interest and ability than before the operation. Then, his motions were extremely slow; he spoke little and was generally negativistic. He now talks of returning to school and of studying airplane designing; he plays a skilful game of checkers and is socially fairly well adjusted. This is the first case on record in which operation was advised and a portion of the brain removed on the basis of an electro-encephalogram which showed localized pathologic electrical activity.

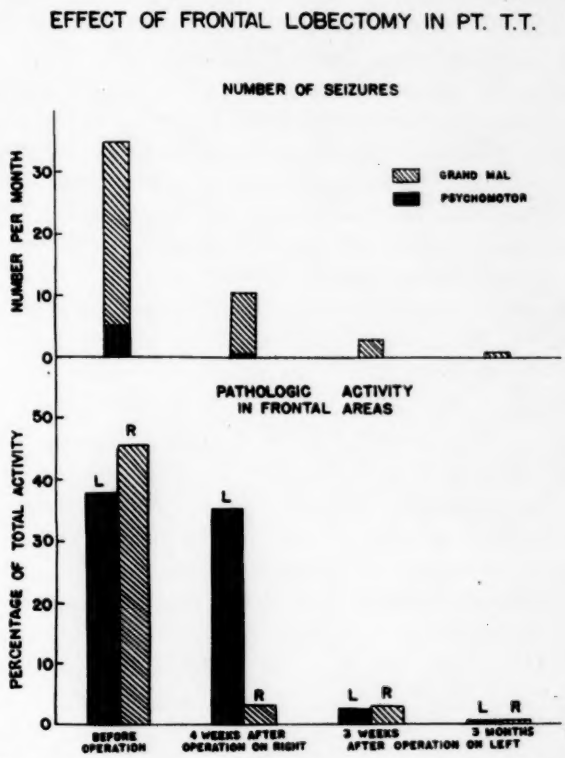

Fig. 6.—Effect on seizures and the pathologic activity of the cortex of bilateral frontal lobectomy in a patient who had independent foci of abnormal activity in both prefrontal areas. The amount of pathologic activity is expressed in percentages of the time that high voltage wave and spike formations were present in the record for the frontal area.

It might have been expected that the operations would have abolished all activity in the frontal areas, but such was not the case; normal and some abnormal activity were still obtainable; it came, presumably, from gray matter surrounding the area of excision. Subsequent subsidence of much of this remaining pathologic activity is encouraging. *R* indicates the right; *L*, the left.

The experience demonstrates that abnormal activity can be treated surgically, with resulting definite clinical improvement. The degree of improvement depends apparently on the completeness of removal of the tissue showing pathologic

activity. It is encouraging to observe in this case that even though some pathologically active tissue was left, the patient's condition and the abnormalities in the electro-encephalogram have continued to improve.[1a]

HOW CAN CEREBRAL DYSRHYTHMIA BE PREVENTED?

One can remove or kill the abnormal nerve cells which produce the pathologic rhythms. An example is the surgical intervention in the case which was just described. One can isolate "sick" cells so that they cannot influence the rest of the brain. This conceivably could be done surgically, but in some cases sedative drugs may be effective. The most familiar anticonvulsant is phenobarbital. This drug appears not only to keep the abnormal disturbance confined to its point of origin but to disorganize the pathologic rhythm and decrease its amplitude. These are probably merely different aspects of the same basic effect; that is, spread of the abnormal electrical activity is interrupted not only between cortical areas but between cells, and probably even between different portions of a single nerve cell.

One can treat the cerebral arrhythmia symptomatically; that is, if the frequency is too fast one can attempt to slow it down, or if too slow one can try to speed it up. The trouble with such measures is that in epilepsy the rate-regulating mechanisms are defective, so that if one tries to overcome a frequency which is too slow, such as in psychomotor dysrhythmia, one may succeed but the frequency may swing far to the fast side, abnormal amplitudes may develop and a grand mal seizure ensue. In line with our observations on this point is the evidence that alcoholic intoxication may precipitate a seizure. Since ether and alcohol have similar accelerator effects, ether convulsions are also to be explained as an extreme accelerator response from a defective rate-regulating mechanism. If, on the other hand, one slows activity, as one may with phenobarbital, in order to prevent a grand mal seizure, the frequency regulation may swing all the way to the slow side, and a psychomotor outburst may ensue. Thus, the frequency-regulating mechanism of the brain in epilepsy behaves like an inverted pyramid; if it is pushed in either direction, it tends to fall all the way over. Probably a better analogy is that of an undamped pendulum, for in the epileptic person regulation of rate is apparently controlled by a mechanism which is likely to oscillate widely if disturbed. Thus, a normal person can shift smoothly from the slow activity of deep sleep to the moderately fast activity characteristic of the waking state, but this is a precarious task

1a. A year after operation, seizures have returned to about half their preoperative frequency. Also, two other patients have had frontal lobectomy, with results to date which are excellent in one case and indifferent in the other.

for the epileptic person. The liability of epileptic patients to have seizures at the time of waking is well recognized. The shift in frequency at that time is the greatest which ever occurs in the normal person. It is not surprising, therefore, that the early part of the morning is the most common time for seizures. We have records to show that in epileptic patients the slow frequencies of deep sleep, as they shift to the fast rates of the waking state, tend to overshoot to the fast side. Sometimes before waking or just after waking there are several instances of such "overshooting," which is quickly corrected; then there follows a swing which is even more extreme, and a grand mal seizure develops. Such overshooting accounts, we believe, for the tendency of epileptic patients to have a series of seizures when phenobarbital medication is discontinued. Overshooting tends also to occur to the slow side. In the normal subject closing the eyes causes cortical activity to become slower, and in two of our patients abnormally slow waves commonly appear as soon as the eyes are closed. These may continue for a short time, and then develops the rapid alternation between fast and slow waves which is characteristic of petit mal (that is, the 3 a second wave and spike), and a clinically characteristic petit mal seizure may occur (fig. 7). We have already reported the converse of this situation in a case in which opening the eyes tended to decrease the amount of petit mal activity and the number of clinically obvious petit mal seizures.

The possibility has occurred to us of improving the environment of the "sick" cells sufficiently to allow them to function as though they were normal, and in two cases we have met with striking, if temporary, success.

In two patients who displayed a large amount of petit mal activity, intravenous injection of a solution of dextrose abolished this activity. That the dextrose had this effect rather than changes in osmotic pressure or altered volume is shown by the fact that considerable improvement was produced in one of these patients when dextrose was taken by mouth but none when a solution of sucrose was injected. Furthermore, in both cases insulin produced marked exacerbation of the pathologic activity (fig. 8). The amount of petit mal activity in these cases tended to be inversely proportional to the level of the blood sugar. It is conceivable that provision of an especially favorable environment for the cells which are "sick" would result in their cure. Since dextrose is the chief fuel of the nerve cell, one certainly should provide sugar in abundance. However, the exceedingly high levels of blood sugar necessary to abolish the pathologic activity is somewhat discouraging, for it is difficult to maintain a high level of available blood sugar over long periods.

For a dozen years it has been known that "blowing off" carbon dioxide from the lungs tends to produce seizures and that inhalation of air rich in carbon dioxide tends to prevent them. This effect is apparently due to a shift in the p_H of the blood reaching the brain.

Recent studies by Lehman [2] have shown that the same relationship exists between carbon dioxide tension and spontaneous discharges in the peripheral nerve as between carbon dioxide tension and petit mal seizures. As we reported in a previous paper, inhalation of carbon dioxide tends to abolish the wave and spike formation characteristic of petit mal (fig. 9). Breathing oxygen was without effect on abnormal waves (fig. 10). Our recent observations show that long-continued breathing of an atmosphere high in carbon dioxide keeps the wave and spike formation in abeyance so long as the carbon dioxide tension remains high. When this tension falls to normal, however, the wave and spike formation characteristic of petit mal again appears. Furthermore, as in many other conditions, there tends to be a sort of "overshooting," or postinhibitory rebound. The more abrupt the change from a high to a normal carbon dioxide tension, the greater the "over-

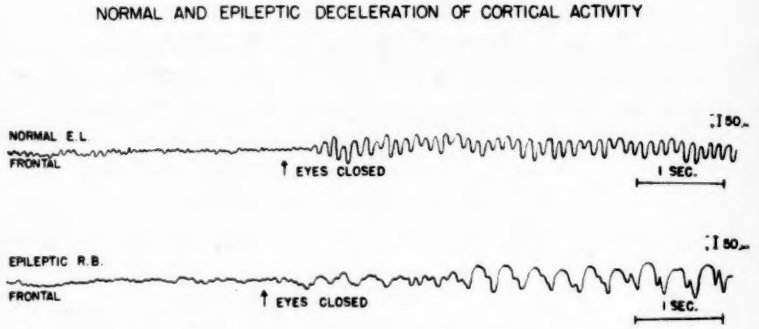

Fig. 7.—Contrast between the normal slowing of cortical frequency when the eyes are closed and the extreme slowing which is observable in some epileptic patients. The record shown here was obtained from a patient who has petit mal seizures. The high voltage, 3 a second wave and spike formation which appears after the eyes are closed is characteristic of petit mal.

This is an example of one type of the abnormal regulation of rate which is characteristic of epilepsy. The opposite situation, in which a procedure causing moderate increase in frequency in the normal subject results in extreme increase in frequency in the epileptic patient, has also been observed.

shooting"—that is, the more nearly continuous the pathologic activity and the greater its voltage. Long-continued breathing of carbon dioxide may completely unbalance the rate-regulating mechanism in epileptic persons, as was evidenced by the fact that in two of the three patients who breathed an increased concentration of carbon dioxide for an hour or more, return to breathing room air was followed by a grand mal seizure after a period of from four minutes to ten minutes. When

2. Lehman, J. E.: The Effect of Changes in Potential on the Action of Mammalian Nerve Fibers, Am. J. Physiol. **118**:600, 1937.

inhalation of carbon dioxide is given as treatment, the carbon dioxide tension should be reduced gradually.

Are there any specialized centers which regulate rate in the central nervous system? The answer to this question is in the affirmative. The sleep center in the diencephalon is a collection of cells so placed and so connected with other centers that changes in the center are

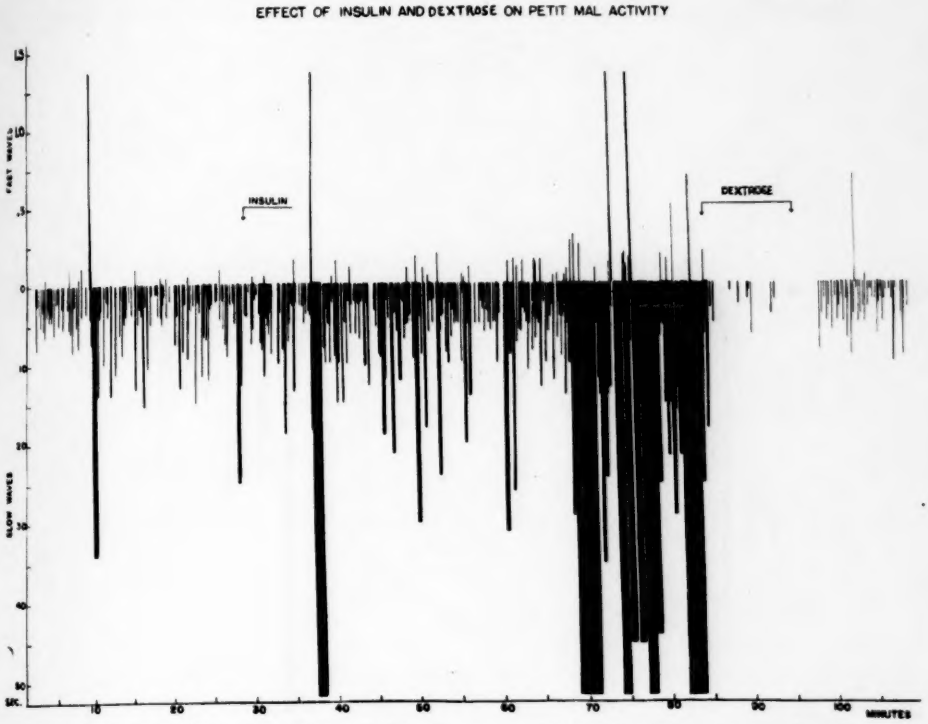

Fig. 8.—Effect of variations in blood sugar on the high voltage wave and spike formation which is characteristic of petit mal. The severity of the abnormal rhythm is to be gaged not alone by the percentage of time that it is present but by the length of each burst of the disturbance. In this figure (and in figures 9 and 10) time has been plotted in two dimensions: first, the regular course of time, from left to right, as abscissas; and second, the number of seconds during which 20 a second spikes were continuously present, as positive ordinates, and the number of seconds during which the 3 a second waves were continuously present, as negative ordinates. As may be seen from the calibrations, the positive time scale is more spread than the negative. The more severe the electrical disturbance, the higher are the vertical lines and the greater is their width. Thus, a third dimension is represented; for besides the time of occurrence and the frequency of pathologic activity, the duration of trains of abnormal rhythms is shown. The shaded area, above the zero line (for the high voltage spikes) and below the line (for the high voltage slow waves) represents the total abnormal activity.

At the point marked *insulin* 40 units was administered. During the period marked *dextrose* 50 Gm. of dextrose in a 50 per cent solution was injected intravenously.

reflected widely as alterations in rate throughout the cortex. In the cat's brain are certain concentrations of tissue in which weak electrical stimulations result in violent and widespread discharges of motor centers. The work of Gibbs and Gibbs [3] on the convulsion threshold of various parts of the cat's brain showed this.

Probably not all brain cells are equally susceptible to injury, and certain cells when injured are more likely than others to discharge abnormally. It is also reasonable to suppose that, because of their

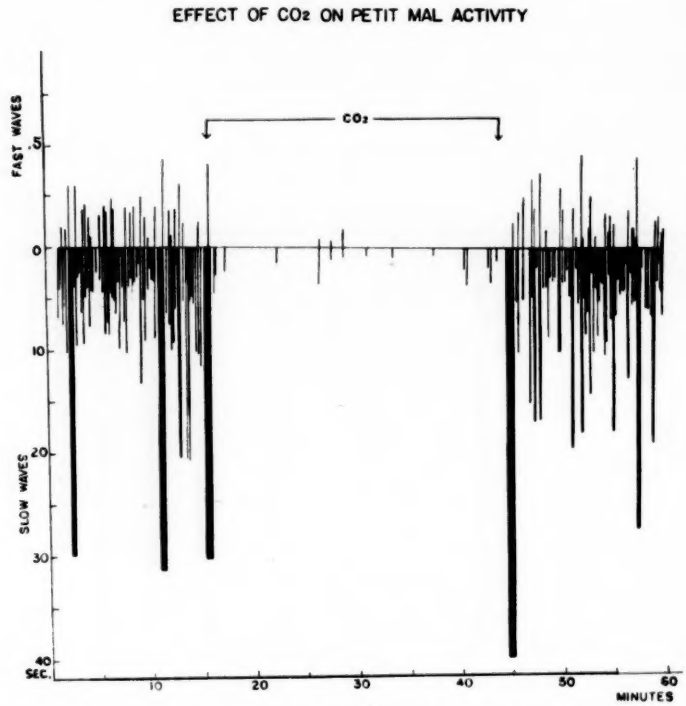

Fig. 9.—Effect of breathing an atmosphere high in carbon dioxide on the high voltage wave and spike formation which is characteristic of petit mal. Values are represented as those in figure 8. The severity of the pathologic activity at any time is indicated by the amount of shaded area; the spikes are represented above zero on the vertical scale, and the high voltage, 3 a second waves, below zero. During the period marked CO_2 the patient was breathing a mixture of 5 per cent carbon dioxide and air.

function, which is largely dependent on fiber connections, certain cell masses are more likely than others to produce subjective or objective symptoms. The question of whether there are "epilepsy centers" resolves

3. Gibbs, F. A., and Gibbs, E. L.: The Convulsion Threshold of Various Parts of the Cat's Brain, Arch. Neurol. & Psychiat. **35**:109 (Jan.) 1936.

itself into that of whether there are centers in the brain. The same basic disturbance of normal rhythm will be called by different names, depending on the center or portion of the brain in which the abnormality arises. Involvement of one center gives "epilepsy"; of another,

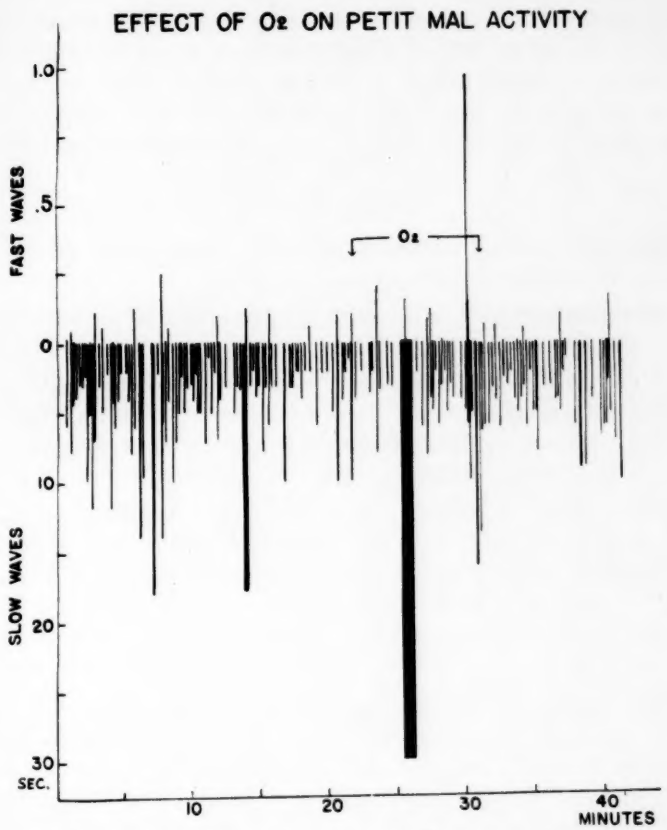

Fig. 10.—Effect of breathing oxygen on the high voltage wave and spike formation which is characteristic of petit mal.

Values are represented as shown in figure 8. The severity of the pathologic activity at any time is indicated by the amount of shaded area; the spikes are represented above zero on the vertical scale, and the high voltage, 3 a second wave, below zero.

During the period marked O_2 the patient breathed pure oxygen. This produced no significant decrease in the pathologic activity. The long run of high voltage, 3 a second waves, indicated by the thick black line in the center of the period during which oxygen was being breathed, may not have been related to the breathing of oxygen; for such bursts occurred occasionally at long intervals during a two hour period used as a control. The same may be said of the large burst of spikes which followed. The appearance of these exceedingly severe disturbances during the breathing of oxygen indicates clearly, however, that this procedure does not prevent pathologic activity of the petit mal type.

choreo-athetosis; of another, parkinsonism; of another, hallucinations; of another, neuralgia, and so on. As has been shown by our studies, the supposed periodic character of epilepsy is not of fundamental significance; in many cases practically constant pathologic activity is shown in the intervals between seizures, and the seizure itself is merely an exacerbation of the condition. Grand mal epilepsy is episodic because activity of the nerve cells in grand mal is so excessive that it cannot be met by the available supply of energy. Periodic acute exacerbations, such as are seen in epilepsy, are not peculiar to epilepsy; they are common to many disorders, ranging from appendicitis to zoopsia.

CONCLUSIONS

1. Epilepsy is the expression of improper functioning of the rhythm-regulating mechanisms of the brain.

2. Abnormalities of rhythm are common to all parts of the nervous system.

3. Abnormalities of rhythm in certain portions of the cortex can be correlated with certain clinical types of epilepsy; a fast rhythm spells grand mal, a slow rhythm psychomotor and an alternating slow and fast rhythm petit mal epilepsy.

4. The symptoms which accompany abnormal electrical activity depend on three factors; first, the function of the area or areas of the brain involved; second, the rapidity of the rhythm (high frequencies producing overactivity and slow frequencies underactivity), and, third, the amplitude of the activity, for on this will depend the intensity of the symptoms.

5. The rate of both normal and abnormal rhythms can be altered by the administration of certain drugs and by changes in the physiologic reactions of the body. Particularly pronounced are alterations of rhythm which accompany extreme changes in the level of dextrose and of carbon dioxide in the blood.

6. In the case of a patient whose abnormal rhythms were present only in sleep and were confined to the frontal area, the anterior portions of both frontal lobes were removed, with subsequent virtual disappearance of abnormal rhythms and great improvement in seizures.

NEURAL CORRELATIONS OF VISION AND THEIR SIGNIFICANCE FOR LOCALIZATION OF TUMORS OF THE BRAIN

A PRELIMINARY REPORT

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There is no general agreement regarding the relative importance of the retinal and the central components in the leveling of sensibility to different intensities of light which is called light and dark adaptation. Although it is probable that in the healthy person light is of more significance than area, the relative importance for acuity of vision of increase in illumination and increase in area merits further study. When vision is impaired as the result of a retinal lesion, it may be that the relative importance of light and of area is altered. When studied by functional tests, the diminution of vision due to papilledema may differ from that due to primary atrophy of the optic nerve, and the relative importance for acuity of vision of light and of area may be altered in cases of lesions in the visual pathways or in the occipital lobes of the brain. Furthermore, in cases of tumor or other localized disease in one cerebral hemisphere, the time required for the dark adaptation of one eye may be different from that of the other. Functional visual tests might therefore be of value for the localization of tumors of the brain. These considerations induced us to make the investigations described in this paper.

TECHNIC

The apparatus and methods used will be described in detail in papers soon to appear.[1] For our present purpose, it is sufficient to state that visual acuity was studied by the use of test objects which were viewed from a distance of 3.75 meters

From the Clinical Research Laboratories of the Neurological Institute of New York.

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Read by title at the Sixty-Third Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 5, 1937.

1. Elsberg, C. A., and Spotnitz, H.: The Sense of Vision: I. A Method for the Study of Acuity of Vision and of Relative Visual Fatigue; II. The Reciprocal Relation of Area and Light Intensity and Its Significance for the Localization of Tumors of the Brain by Functional Visual Tests; III. A Theory of the Functions of the Retina, Bull. Neurol. Inst. New York **6**:233-267, 1937.

through a red filter (Wratten F 29). Most of the studies were made with red light beyond 610 millimicrons of the spectrum, although some were carried out with white light. The test objects consisted of white squares on a black background, and the size of the squares varied from 9 to 40 mm. In order to study internal contrast, black squares within white squares were used. At the distance from which the test objects were viewed, they subtended visual angles of from 8 to 36 minutes and were well within foveal vision.

The intensity of illumination of the test objects was varied by means of a special rheostat which controlled the electric current to a 30 watt red glass bulb, from which the light was thrown on the test object by a reflector. The rheostat scale was marked in millimeters, and an automatic switch made it possible to decrease the intensity of light to zero in an almost continuous series. The possible margin of error with this apparatus is about 10 per cent.

The intensity of light used for illumination of the test object was measured by a photometer which established the values in foot candles. The smallest test object that could be seen as a luminous spot was the brightness threshold for the illumination that had been used. Thresholds or minima for both the size of the

TABLE 1.—*Threshold Intensity of Light and Constants for Binocular Vision in Two Persons*

Size of Object, Mm.	Area, Sq. Mm.	Cube Root of Area (A)	H. S. Minimum Intensity (I)	H. S. A × I	C. A. E. Minimum Intensity (I)	C. A. E. A × I
40	1,600	11.7	3.3	38.61	5.1	54.65
35	1,225	10.7	3.7	39.59	5.5	58.85
30	900	9.65	4.0	38.60	6.0	57.90
25	625	8.55	4.3	36.77	6.4	54.72
20	400	7.37	4.9	36.13	6.8	50.14
18	324	6.87	5.3	36.41	7.9	54.27
15	225	6.13	5.7	34.94	9.3	57.01
12	144	5.24	6.6	34.54	10.4	54.49
9	81	4.33	8.0	34.64	12.9	55.85

test object and the light intensity were established for monocular and binocular vision. The tests were made in a dark room, and ten minutes was always allowed for dark adaptation.

RESULTS OF TESTS FOR BRIGHTNESS ACUITY ON HEALTHY PERSONS

Before the visual tests were used for patients suspected of having tumor of the brain or in whom a tumor had been verified, a large number of investigations were made on healthy persons.

1. White squares varying in size from 9 to 40 mm. were used as test objects, and the minimum intensity of light required to see each test object was ascertained. When the relations between the area of the test object and the threshold intensity of light were compared, it was found that there was a constant logarithmic relation between the two. The product of the cube root of the area and the threshold intensity of light was a constant for each person. In other words, the product of the cube root of the area and the minimum intensity of light required to see the object was the same for all the test objects (table 1).

2. When white squares of 40 mm. with black squares within the white ones were used as test objects, the product of the square root of the white area and the minimum intensity of light was a constant (table 2).

TABLE 2.—*Threshold Intensity of Light and Constants for Binocular Vision in Two Persons*

				H. S.		C. A. E.	
Object	White Area, Sq. Mm.	Black Area, Sq. Mm.	Square Root of White Area ($\sqrt{WA}$)	Minimum Intensity (I)	$\sqrt{WA} \times I$	Minimum Intensity (I)	$\sqrt{WA} \times I$
1	1,600	...	40.0	4.3	172.0	5.2	208.0
2	1,200	400	34.7	4.8	166.8	5.8	201.3
3	800	800	28.3	6.0	169.8	6.9	195.3
4	400	1,200	20.0	8.4	168.0	9.9	198.0

TABLE 3.—*Threshold Intensity of Light and Constants for Binocular Vision in Two Persons*

			H. S.		C. A. E.	
Object	White Area (A), Sq. Mm.	Black Area, Sq. Mm.	Minimum Intensity (I)	A × I	Minimum Intensity (I)	A × I
1	81	..	7.45	603.5	12.6	1,020
2	73	8	8.3	605.9	14.4	1,051
3	65	16	9.7	630.5	16.0	1,040
4	57	24	10.8	615.6	18.0	1,026
5	49	32	12.0	588.0	20.4	1,000
6	32	49	16.2	518.4	25.6	819.2

TABLE 4.—*Threshold Intensity of Light and Constants.*

					C. A. E.†	
Object	H. S.* Intensity (I)	Square Root of Black Area ($\sqrt{BA}$)	$\frac{\sqrt{BA}}{I}$	Object	Square Root of Black Area ($\sqrt{BA}$)	$\frac{\sqrt{BA}}{I}$
1	...	...	....	1	...	...
2	8.3	2.8	0.34	2	5.8	3.4
3	9.7	4.0	0.41	3	8.3	3.4
4	10.8	4.9	0.45	4	9.9	3.5
5	12.0	5.7	0.47			

* Compare table 3.
† Compare table 2.

3. When white squares of 9 mm. with internal contrast were used, the product of the white area and the minimum intensity of light was a constant (table 3).

4. For all test objects with internal contrast, the square root of the black area divided by the light intensity or the light intensity divided by the square root of the black area was a constant (table 4).

These varying relations between area and the minimum of light required for vision were suggestive of the functional relationships of the cones, bipolar cells and ganglion cells of the retina and raised the question whether the single root, square root and cube root constants for the objects we used might somehow be associated with the relative amounts of energy received at the cones, bipolar cells and ganglion cells of the retina.

Summation effects at the retina have frequently been described. That such effects are compatible with the amount of light received by the retina was indicated in our experiments. In order to obtain constants for threshold vision, it was found necessary to multiply some root of the white area by the minimum intensity of light required. The fact that in order to obtain constants for objects with internal contrast it was necessary to divide the light intensity by the square root of the black area suggested that an inhibitory mechanism might be an important factor in the perception of such objects.

The existence of an inhibitory mechanism in the retina is probable. Centrifugal fibers are known to end around the amacrine cells and to have synaptic relationships with the bipolar cells (Cajal, Greeff and others). The regenerating fibers from the distal end of the proximal segment of a divided optic nerve (Tello) are further proof of the presence of centrifugal fibers in the nerve. Granit and Theman, among others, showed that the first result of stimulation of the eye of the frog by light is a wave of inhibition in the optic nerve. Arey found that during dark adaptation centrifugal fibers play an important part in the alterations of the myoids of the cones and in the arrangement of retinal pigment.

As already mentioned, the results of our studies suggested that first root relationships might be representative of constant effects at the cones (first neuron), second root relationships of constant effects at the bipolar cells (second neuron) and third root relationships of constant effects at the ganglion cells (third neuron). That $\frac{\text{Intensity}}{\sqrt{\text{Black Area}}}$ is a constant for a black surrounded by a white area suggested that the inhibitory impulse transmitted by centrifugal fibers might be effective at the second, or bipolar, neuron of the retina. This appeared to be in accord with the fact that the centrifugal fibers end around the amacrine and bipolar cells.

Calculations were made of the extent of the inhibition for test objects with internal contrast. The calculations were based on the assumption of the root theory of the function of the different retinal elements, i. e., that single root relationships are indicative of constant effects at the cones, second root relationships of constant effects at the bipolar cells and third root relationships of effects at the ganglion cells of the retina.

and, furthermore, that retinal inhibition is a function of second root relationships at the bipolar synapses.

On this basis, the number of bipolar cells influenced by the black area of a contrast object is indicated by $\sqrt{BA}$, and the number of bipolar cells influenced by the white area of any object, by $\sqrt{WA}$. Likewise, $\sqrt[3]{BA}$ can be used to express the number of ganglion cells influenced by the black area, and $\sqrt[3]{WA}$, the number of ganglion cells influenced by the white area.

We have already stated that the product of the cube root of the area and the intensity of light required for threshold vision ($\sqrt[3]{WA} \times I$) was a constant for the white squares that were used as test objects. This formula expresses the energy which reaches the ganglion cells of the retina and is transmitted to the calcarine cortex. This amount of energy is, however, not the same as the total amount of light from a square test object which affects the cones. The total amount of light is clearly the product of the light intensity and the total area of the test object ($A \times I$), but this formula cannot be used to indicate the light energy that is effective on the ganglion cells of the retina, which is $\sqrt[3]{A} \times I$.

It is known that if an area of the retina is stimulated with light, the sensitiveness of the surrounding area is altered. This is shown, for example, in the illustration of black and white contrast given by Hering. The same fact was demonstrated in our tests for visual acuity for brightness. If one looks at a contrast object—a black square within a white square—the purest white is at the junction of the white and the black, and the purest black, at the junction of the black and the white. Further out, in the white area, the color appears slightly gray, and near the middle of the black area the black is gray-black. There is, therefore, an influence both of the black area on the white and of the white area on the black.[2] As stated by Parsons, this reciprocal physiologic activity is analogous to Sherrington's reciprocal innervation.

With objects having internal contrast the light intensity that is required for threshold vision is greater than that with objects of the same size having no internal contrast. Our investigations have shown that this greater amount of energy may be expressed by the formula $I \times \frac{\sqrt[3]{BA}}{\sqrt[3]{WA}}$, in which I is the intensity of light required for threshold

2. This is in accord with the view expressed by Eccles and Sherrington in their studies on inhibition of the flexor reflex (Proc. Roy. Soc., London, s.B **109:** 91-113, 1931). They made the following statements: "When the central excitatory state and central inhibitory state are opposed to each other, there is an inactivation of certain quantities of each. This mutual inactivation is likely to be quantitative, in which case there is true algebraic summation between the c.e.s. and c.i.s. of a motoneuron . . . It may be that there is a quantitative interaction between the c.e.s. produced by one excitatory impulse and the c.i.s. produced by one inhibitory impulse, but such a relationship is at present pure hypothesis."

vision and $\frac{\sqrt[9]{BA}}{\sqrt[9]{WA}}$ the relative number of ganglion cells influenced by the black and the white area of a contrast object. Therefore the formula $I \times \frac{\sqrt[9]{BA}}{\sqrt[9]{WA}}$ expresses the reciprocal influence of the black and white areas on the amount of light necessary for threshold vision. If this quantity is subtracted from the total amount of energy ($\sqrt[9]{WA} \times I$) needed for threshold vision of a white object, the result will express the energy required for threshold vision of an object with internal contrast. This formula $\sqrt[9]{WA} \times I - (I \times \frac{\sqrt[9]{BA}}{\sqrt[9]{WA}})$ gave constant values for the series of objects we used in our visual tests, whether these were white squares or white squares with internal contrast. For the objects used by us, the formula for foveal vision is, therefore, $\sqrt[9]{WA} \times I - (I \times \frac{\sqrt[9]{BA}}{\sqrt[9]{WA}}) = C$, in which C is a constant.

The theory just outlined and the formula given are, therefore, suggested to explain the process of retinal inhibition and its influence on visual acuity at the fovea.

The theory of inhibition at the retina may also explain the character of the action currents in the optic nerve after stimulation of the retina by light. Adrian and his co-workers demonstrated that an increase of light acting on the isolated eyes of the eel caused an increase in intensity of the current in the retina, while in the optic nerve there was an increase in the number of impulses but not in intensity. If it is accepted that the first effect of retinal stimulation by light is an increase in the resistance at the synapses of the bipolar cells and that this primary inhibition is proportional to the light intensity, an increase of light would cause greater inhibition. This would, however, be overcome more rapidly the more intense the stimulation, so that the end effect would be increased frequency of impulses in the optic nerve, and therefore increased brightness.

This explanation of the interplay between stimulation of the retina by light and inhibition at the bipolar synapses and the theory of the functional relations of the cones, bipolar cells and ganglion cells appear to agree with the observed anatomic and physiologic facts of the retina and the optic nerves. It is in harmony with the all or nothing law of conduction of the nerve impulse. It attributes the increase in visual acuity produced by increase in light intensity, variations in the frequencies of impulses in the optic nerves and the effect of contrast to the interaction of different amounts of excitatory and inhibitory energy at the synapses of the bipolar (and amacrine) and ganglion cells of the retina. The result is a varying frequency of impulses in the optic nerves, which impulses are in turn transmitted to the visual centers and result in the phenomena of vision.

RESULTS OF TESTS FOR DARK ADAPTATION IN HEALTHY PERSONS

When dark-adapted eyes are exposed successively to a bright light and then to the original dim light, there is a definite period during which a threshold test object cannot be seen. This is the time required for dark adaptation. There are many facts to support the belief that the refractory period is the result mainly of central, rather than retinal, adaptation.

In order to study this aspect of the subject, we investigated the effects of stimulation with bright light of each retina separately and of the two eyes together on the refractory period in monocular and in binocular vision.

One or the other eye or both eyes together were exposed for fixed periods to a bright red light (from a 30 watt bulb, 40.5 cm. from the eye and viewed through a Wratten filter); the time which elapsed between the stimulation with bright light and the return of ability to see the threshold object was the duration of the refractory period. Each test was repeated at least three times, with intervals of rest of one minute between each test.

A summary of the results of the tests is given in the following paragraphs.

1. *Effects of Monocular Stimulation on Monocular Relative Fatigue and of Binocular Stimulation on Binocular Relative Fatigue.*—For both monocular and binocular vision, the duration of the refractory period was dependent on (*a*) the intensity of illumination of the test object; (*b*) the size of the test object; (*c*) the intensity of stimulation by the brighter light, and (*d*) the duration of stimulation by the brighter light.

2. *Duration of Monocular Fatigue Due to Monocular Stimulation as Compared with Duration of Binocular Fatigue Due to Binocular Stimulation.*—The duration of the refractory period was always longer when the retina of one eye was exposed to the stimulating light and the test object was viewed with that eye alone than when both eyes were simultaneously exposed to light and the test object was viewed with both eyes.

3. *Duration of Monocular Fatigue After Binocular Stimulation as Compared with Duration of Binocular Fatigue After Binocular Stimulation.*—If both eyes are exposed to the stimulating light but the test object is viewed with only one eye, the duration of the period during which the object is invisible is always shorter than in monocular vision after monocular stimulation and longer than in binocular vision after binocular stimulation.

These results are significant for binocular as compared with monocular vision. They demonstrate that in the process called dark adaptation, recovery of vision is more rapid when both eyes are used than when vision is monocular. In passing from a bright into a dimmer light the ability to see objects is regained more rapidly if both eyes are used, no

matter whether one or both eyes had been exposed to the bright light. This represents an important fact in the physiology of vision. The results of the tests in which the effects of binocular stimulation on binocular and on monocular vision were compared cannot be explained on the basis of the retinal effect of light. The differences in the results of the tests must be connected with the visual side of the process and with the quantity of impulses required by the brain for vision at the threshold in monocular and in binocular vision.

RELATIVE INTENSITY OF LIGHT REQUIRED FOR THRESHOLD VISION IN DIFFERENT PARTS OF THE FOVEA

The relative importance of light for vision depends not only on the intensity of the light but on the part of the retina affected by the light. The sensation of brightness must be proportional to the number of percipient elements that are in action. Adrian [3] expressed this fact clearly:

> Unless the receptors are very far apart, an intense stimulus will excite more of them than a weak stimulus, and the complete message which reaches the central nervous system may therefore vary with the intensity of the stimulus. We ought, therefore, to think in terms of areas containing many receptors and not in terms of the single receptor when we are trying to estimate what sort of information reaches the central nervous system.

All the recent investigations, both anatomic and physiologic, indicate that, functionally at least, the number of cones that are affected by light varies in different parts of the retina and, in particular, in different parts of the fovea. The number of cones functionally connected with each retinal ganglion cell differs in different parts of the fovea. In the central part there is in all probability a unit relation, while farther from the center of the fovea the numerical relation of cones to ganglion cells in terms of function is different.

In order to study this aspect of the subject, we made a series of tests with objects in which the total area was kept constant while the distance of the white area which reflected the light was farther and farther from the fixation point.

In what follows a few illustrations of the test objects that were used and of the results of the tests are given. In one series the test objects consisted of three square areas in each of which the light was reflected from an area of 800 sq. mm., viz., (1) a white square of 800 sq. mm.; (2) a square of 1,225 sq. mm. with an inner black square of 425 sq. mm., and (3) a square of 1,600 sq. mm. with an inner black square of 800 sq. mm.

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3. Adrian, E. D.: The Basis of Sensation, New York, W. W. Norton & Company, 1928.

The threshold intensities of light required by two subjects are shown in table 5.

In another series of tests the area from which light was reflected was 36 sq. mm. (table 6).

In both series of tests (tables 5 and 6) the number of light units required for threshold vision of brightness became larger as the white area was farther from the fixation point. This may be the result not only in part of an inhibitory effect of the inner black on the outer white area but in part of the greater distance of the white area from the center of the fovea. These results suggest that in and near the center of the fovea fewer cones are functionally related to each ganglion cell than farther out. This is the generally accepted view.

TABLE 5.—*Threshold Intensities of Light for Two Subjects*

	Size of Test Object, Mm.	Total Area, Sq. Mm.	White Area	Light Intensity for Subject A	Threshold Vision Subject B
1	28.3	800	800	5.9	4.3
2	35.0	1,225	800	6.2	5.2
3	40.0	1,600	800	6.6	5.6

TABLE 6.—*Threshold Intensities of Light with an Area of 36 Sq. Mm.*

Size of Test Object, Mm.	Total Area, Sq. Mm.	White Area	Light Intensity for Subject A	Threshold Vision Subject B
6	36	36	24.8	12.6
8	64	36	26.0	17.6
9	82	36	32.4	19.5

USE OF FUNCTIONAL VISUAL TESTS FOR STUDY OF LOCATIONS OF LESIONS IN THE RETINA

In the attempt to devise functional visual tests for the localization of tumors and other diseases of the brain, the reciprocal relation of area and light must be investigated. The diminution of vision produced by papilledema involves all layers of the retina, while that which results from primary atrophy of the optic nerve involves primarily and more especially the retinal ganglion cells. It is reasonable to expect, therefore, that in papilledema the relative importance of light and area should differ from that in primary atrophy of the optic nerve. Furthermore, by functional visual tests it ought to be possible to gain information regarding the retinal component in diminution of vision and to determine the part of the fovea that is most affected by the retinal lesion.

In a series of investigations on normal persons with white squares of various sizes, we ascertained the intensity of light required for threshold vision of each test object. It was found that the product of the cube root of the area and the required light intensity ($\sqrt[3]{A} \times I$) was a constant quantity for all the objects used except those the area of which was less than 81 sq. mm. When the tests were applied to patients with retinal lesions, we found that the formula $\sqrt[3]{A} \times I = C$ no longer held. Each eye was examined separately with two test squares, one of 40 and the other of 9 mm. If the product of the cube root of the area and the required light intensity was larger for the object the area of which was 1,600 sq. mm. than for that the area of which was 81 sq. mm., it signified that the outer parts of the fovea were more affected than the central area. If the product was larger for the smaller object, it signified that the changes were more marked in the central part of the fovea. The results of a few illustrative tests are given in the following cases.

CASE 1.—S. M. Pituitary tumor, not associated with visual disturbance or changes in the fundi.

Area of Test Object, Sq. Mm.	Threshold Light (Foot Candles)		$\sqrt[3]{A} \times I$	
	Right	Left	Right	Left
1,600	4.5	5.1	52.65	59.67
81	12.3	13.8	53.01	59.47

CASE 2.—H. L. Pituitary tumor, associated with bitemporal hemianopia and primary atrophy of the optic nerve.

Area of Test Object, Sq. Mm.	Threshold Light (Foot Candles)		$\sqrt[3]{A} \times I$	
	Right	Left	Right	Left
1,600	5.65	5.65	66.1	66.1
81	22.8	54.3	98.72	235.12

CASE 3.—H. S. Left temporoparietal glioma, associated with high grade papilledema.

Area of Test Object, Sq. Mm.	Threshold Light (Foot Candles)		$\sqrt[3]{A} \times I$	
	Right	Left	Right	Left
1,600	5.7	5.7	66.69	66.69
81	16.2	17.0	69.82	73.27

CASE 4.—L. P. Acoustic neurinoma on the left, associated with high grade papilledema.

Area of Test Object, Sq. Mm.	Threshold Light (Foot Candles)		$\sqrt[3]{A} \times I$	
	Right	Left	Right	Left
1,600	3.5	4.05	40.95	47.4
81	12.9	13.8	55.6	59.5

CASE 5.—H. S. Retinitis on the right side, of unknown cause.

Area of Test Object, Sq. Mm.	Threshold Light (Foot Candles)		$\sqrt[3]{A} \times I$	
	Right	Left	Right	Left
1,600	30.8	5.1	360.0	59.67
81	21.6	12.6	93.0	54.55

In case 1 the values for each eye were constant, which indicates that as far as the retina was concerned, vision was normal. In case 2 the values for $\sqrt[3]{A} \times I$ were not the same as those for the two test objects. The values were greater for the 81 mm. object, indicating that the central part of the fovea was most affected. The lesion was most advanced in the retina of the left eye.

In cases 3 and 4 there was the same condition, but the retinal lesion, which involved especially the central part of the fovea, was not as marked as that in case 2.

In case 5 the retinal lesion on the right had interfered more markedly with the functions of the outer parts of the fovea, in the area subtended by a visual angle of between 8 and 36 minutes, than with those of the central part of the fovea. However, the latter area was also involved, as shown by the high value (93) for the 81 mm. test object.

These few examples of the results of the tests show that in cases of retinal lesion functional visual tests can give information regarding the parts of the fovea the function of which has been most interfered with. The full report on these studies will be given after we have gained a larger experience.

USE OF FUNCTIONAL VISUAL TESTS FOR LOCALIZATION OF SUPRATENTORIAL TUMORS OF THE BRAIN

Some of the methods described in this paper have been used for patients with suspected or verified tumor of the brain or with other intracranial lesions.

For this purpose, the effects of stimulation of each eye by bright light were compared. The test object consisted of a large white and black contrast square. The total area of the square was 6,400 sq. mm., and the area of the inner black square was 4,800 sq. mm. The minimum of light required for vision with each eye was first ascertained, and for each eye in each test the test object was illuminated by light the intensity of which was 20 per cent greater than that required for threshold vision.

The steps of the procedure were as follows: The duration of the refractory period for the right eye was first established. This was the average of the results obtained in three successive tests for the time which elapsed between stimulation of the eye by bright light and the return of ability to see the test object illuminated by the dim light. The right eye was stimulated for fifteen seconds by a brighter light, and the subject then stated the moment when the test object (illuminated by the light the intensity of which was 20 per cent above the threshold) could again be seen.

The same tests were then carried out with the left eye.

In addition, we studied the effects of flickering light on the duration of the refractory period. For this purpose, each eye was exposed to a flickering light for thirty seconds, during which the total stimulation was fifteen seconds and the total of intervals between the flickers fifteen seconds. When the flickering light is used, the eye is stimulated whenever the light is on and is recovering from the effects of the light during the periods when the light is out. In the normal subject the duration of the refractory period after fifteen seconds of flicker should be shorter than after fifteen seconds of continuous light.

SUMMARY AND CONCLUSIONS

In summary, therefore, the tests consisted of the establishment of the average durations of the refractory period for each eye when exposed to a continuous and when exposed to a flickering light for fifteen seconds.

Up to the present about fifty patients have been tested. The following tentative conclusions were arrived at:

1. In cases of supratentorial tumor the duration of the refractory period after stimulation by continuous light is longer in the eye contralateral to the affected hemisphere.

2. When the lesion is in the frontal lobe the duration of the refractory period after stimulation of the homolateral eye with flickering light is longer than that after continuous stimulation of the same eye.

3. When the lesion is in the parietal or the occipital lobe, the duration of the refractory period after stimulation of the homolateral eye with flickering light is shorter than that after continuous stimulation of the same eye.

The functional tests described in this report will be used on a large number of patients with suspected or verified intracranial diseases. The results thus far obtained appear to indicate that the tests are of value for localization of supratentorial disease, but a much larger experience is necessary before a more definite statement can be made regarding their value.

CONTRIBUTION TO PROBLEM OF CUTANEOUS LOCALIZATION IN MAN

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In 1931 Pritchard [1] showed that localization of stimuli is more accurate when the skin is touched with a von Frey hair than when a warm sensation is elicited without involving the contact of a stimulator with the skin. From these experiments he concluded:

> Accurate localization of cutaneous stimulation is possible when the sensibility to touch is present and is in abeyance when this form of sensibility is absent.

As the experiments to be described show, there is a significant difference in the accuracy of localization between experiments involving and those excluding stimulation of sensory endings in the skin by direct contact. In Pritchard's experiments, however, two types of sense organs were involved. In the first group of his experiments, in which von Frey hairs were used, the pressure end-organs which elicit touch sensation were stimulated, and in the second group the end-organs for the warmth sense. Moreover, in none of the experiments were the sense organs in the skin actually located and stimulated. The skin was treated as if there were not a punctiform distribution of cutaneous sense organs, contrary to the view which is generally accepted today. This idea of the presence of specific end-organs in the skin, based largely on the classic investigations of von Frey, has obtained important corroboration by more recent experiments of Bazett and his collaborators,[2]

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1. Pritchard, E. A. Blake: Brain **54**:350, 1931.

2. Bazett, H. C.; McGlone, B.; Williams, R. G., and Lufkin, H. M.: Sensation: Depth, Distribution and Probable Identification in Prepuce of Sensory End-Organs Concerned in Sensations of Temperature and Touch, Arch. Neurol. & Psychiat. **27**:489 (March) 1932. Bazett, H. C., and McGlone, B.: Studies in Sensation: II. The Mode of Stimulation of Cutaneous Sensations of Cold and Warmth, ibid. **27**:1031 (May) 1932.

as well as by the work of Heinbecker, Bishop and O'Leary,[3] who showed that different groups of nerve fibers have different anatomic and physiologic characteristics (size of fibers and conduction rate). In view of this work, it seems necessary that any investigation from which conclusions can be drawn in regard to the physiologic function of cutaneous senses should be based on the stimulation of cutaneous sense organs in which these sense organs have been accurately located. Furthermore, proper evaluation of touch or other cutaneous sensations for accuracy in cutaneous localization is possible only if nontactile and tactile stimulation involve the same sense organ. For this reason, the following investigation was undertaken, in order to determine the error in cutaneous localization in two groups of experiments involving the warmth and the pain sense, respectively. In each group tactile and nontactile stimulation of the sense organs was employed.

METHOD

The volar surface of the left forearm was prepared by shaving an area approximately twice the size of the rubber stamp which was applied. The stamp measured 8 by 4 cm., with the long dimension in the axis of the forearm. The stamp was divided into squares of 64 sq. mm. each. The same stamp was used for recording the protocols (compare Gellhorn and his associates[4]).

The subject, blindfolded throughout the experiment, was comfortably seated in a room at about 20 C., free from drafts and disturbances. The supinated left forearm rested in a comfortable position on small sand-bags on a table. With a round-tipped glass pointer in his right hand the subject indicated the point which he thought had been stimulated.

Warmth spots within the stamped area were located by lightly passing a temperator of from 50 to 55 C. over the skin. The subject indicated when he perceived a definite sensation of warmth. Three such regions to which the subject responded consistently were located, and the most sensitive point in each area was selected for subsequent stimulations. The same temperator was used for tactile warmth stimulation.

Before each stimulus a signal was given, warning the subject to concentrate. As soon as he perceived a warmth sensation, which in all cases occurred within a second or so, the subject proceeded to localize. Each point was stimulated ten times, making a total of thirty trials for each experiment. The subject was instructed to localize the stimulated points only when a definite warmth sensation and nothing else was perceived. For nontactile stimulation of the warmth spot we followed Pritchard's method by using a fine platinum wire loop which was shielded with the exception of its tip and could be accurately set directly above and within 1 mm. of any chosen point on the surface of the skin. By means of a telegraph key a current of from 1.5 to 4.5 volts was passed through the loop, heating it sufficiently to produce a warmth stimulus by means of radiant heat at the point over which it was placed.

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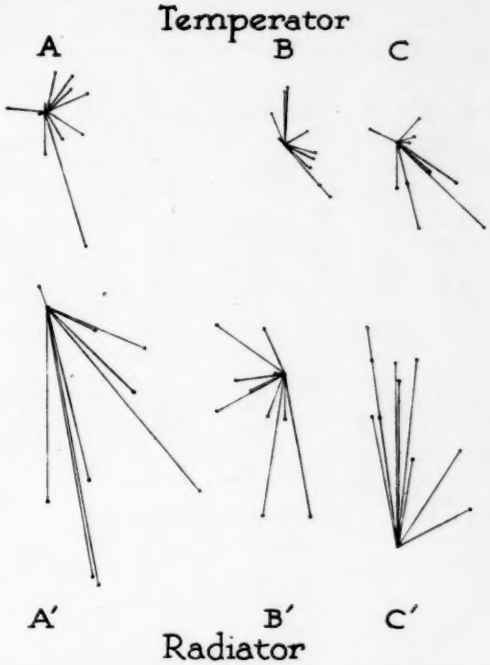
3. Heinbecker, P.; Bishop, G. H., and O'Leary, J.: Pain and Touch Fibers in Peripheral Nerves, Arch. Neurol. & Psychiat. **29**:771 (April) 1933; Analysis of Sensation in Terms of Nerve Impulse, ibid. **31**:34 (Jan.) 1934.

4. Gellhorn, E.; Gellhorn, H., and Trainor, J.: Am. J. Physiol. **97**:491, 1931.

If the subject perceived any pain or touch sensation, the trial was excluded and a different point was used for the next trial. A minimum interval of about a minute was allowed between trials. Each of three points used in the tactile warmth trials were stimulated ten times, and again the errors of localization were recorded.

In order to elicit pain sensations, the skin was stimulated with a von Frey esthesiometer in which the usual horsehair had been replaced by a piece of steel piano wire, 7 cm. long and sharpened to a point. A constant intensity of stimulus was obtained by producing a maximal bend in the wire at each application. Ten pain points were selected which, on stimulation, reacted with nothing but a pain sensation.



Errors in localization of three warmth spots on the volar surface of the forearm. These spots were stimulated with a temperator involving a "tactile" warmth sensation (*A*, *B* and *C*) and then with radiant heat eliciting a "nontactile" warmth sensation (A^1 B^1 and C^1). The records are reproduced at their original size.

The apparatus used for nontactile warmth stimulation was employed for nontactile pain. The wire tip was permitted to become hotter, and the stimulation was continued until in each case a pain sensation was perceived. In the experiments with tactile and those with nontactile pain the same ten points were used. Each point was stimulated three times and the results recorded in the same way. The experiments were carried out on two of us (M. and K.), after a long period of training.

RESULTS

The figure shows the typical differences obtained in an experiment involving the warmth sense. It is apparent that the error in localization

is much greater in the nontactile than in the tactile stimulation experiments. The type of error in localization is similar to that observed in earlier experiments (Gellhorn, Gellhorn and Trainor [4]), the greatest deviation taking place in the longitudinal axis of the arm. A complete summary of all experiments carried out is given in table 1. It shows that localization is consistently much better in the tactile than in the nontactile experiments, the average increase in error in the nontactile group being more than 100 per cent.

The second group of experiments concerns the pain sense. A summary is given in table 2. Here too is found a greater error in localization in the nontactile than in the tactile experiments, but the difference is

TABLE 1.—*Comparison of Average Errors of Localization with Tactile and Those with Nontactile (Radiant) Warmth Stimuli*

Experiment No.	Subject	Tactile Warmth Stimuli				Nontactile Warmth Stimuli				Percentage Increase
		A*	B*	C*	Average	A*	B*	C*	Average	
2	M	6.35†	6.05	6.30	6.23	15.95	19.30	24.25	19.83	218.3
4	M	7.70	8.65	5.65	7.33	16.40	10.70	32.65	19.92	171.8
6	M	7.35	8.80	15.30	10.48	12.55	11.45	28.30	17.43	66.4
8	M	7.85	6.70	8.50	7.68	27.39	11.40	25.00	21.26	176.5
10	M	7.90	6.35	9.90	8.05	28.85	13.50	17.60	19.98	148.2
12	M	6.75	6.60	9.55	7.63	16.75	21.35	24.40	20.83	173.0
3	K	14.70	15.85	15.75	15.43	13.85	33.25	37.75	28.28	83.2
5	K	9.65	7.45	11.50	9.53	13.55	18.05	19.15	16.92	77.5
7	K	10.35	9.90	10.10	10.12	27.80	17.05	17.35	20.73	104.9
9	K	11.10	13.10	11.70	11.96	13.36	16.31	15.86	15.18	26.9
11	K	12.15	11.00	9.40	10.85	17.85	9.15	16.85	14.62	34.8
Mean					9.57				19.54	104.0

* A, B and C are three points.
† Numbers represent the mean error expressed in millimeters, for ten localizations.

smaller and amounts to 43 per cent on the average, one experiment showing no significant change and one a decrease in error, whereas the rest show a typical increase.

The intensity of pain elicited by nontactile stimulation could not be kept constant, since it depended greatly on the quickness of the experimental subject to react, which prompted the experimenter to interrupt the current. For that reason, the experiments are listed in two groups involving "ordinary" and "intense" pain, the first being of approximately the same intensity as that obtained in the tactile experiments and the second considerably greater. As the table indicates, in the nontactile experiments there is no significant difference between the error in localization with low and that with high intensity of pain. This is in agreement with observations by Mayer.[5] In view of this fact, it seems permissible to summarize all nontactile experiments recorded

5. Mayer, B.: Ztschr. f. Psychol. u. Physiol. d. Sinnesorg. (Abt. 2) **56:** 141, 1924.

in table 2 and to state that there is a significant difference in the error of pain localization, which is again in favor of tactile localization.

The question is how this result can be explained, since in both cases the same sense organ is involved and since differences in the intensities of stimuli which might occur do not lead to significant changes in the error of localization. One might think first of the possibility that the stimulation of sense organs in the skin by radiant heat was not as accurate as that in which the sense organ in the skin was actually touched. The fact, however, that the stimulator was brought to a distance of not more than 1 mm. above the pain or warmth spot and was well shielded, thereby preventing a significant spread in excitation, seems

TABLE 2.—*Comparison of Average Errors of Localization with Tactile and Those with Nontactile (Radiant) Pain Stimuli*

Experiment No.	Subject	Tactile Pain	Nontactile Pain				Percentage Increase
			Ordinary	Intense	$\frac{I^* - O^\dagger}{O} \times 100$	Average	
15	M	4.83‡	.....	.....	....	10.18	110.4
17	M	6.98	.....	.....	....	9.17	31.4
19	M	7.87	9.82	9.39	−4.4	9.62	22.2
21	M	9.07	10.20	11.50	12.7	10.72	18.2
23	M	7.38	10.58	12.22	15.5	11.08	50.2
25	M	9.07	7.50	6.77	−9.7	7.28	−19.8
14	K	5.65	.....	.....	....	9.18	62.5
16	K	5.51	.....	.....	....	5.65	2.5
18	K	5.28	.....	.....	....	8.48	60.6
20	K	5.48	9.19	8.56	−6.9	9.00	64.3
22	K	5.30	10.44	8.58	−17.8	9.69	82.8
24	K	5.35	10.35	9.80	−5.3	10.17	90.1
26	K	4.96	7.35	8.54	16.2	7.96	60.5
Mean.....		6.36				9.09	+43

* I indicates intense nontactile pain.
† O indicates ordinary severity of nontactile pain.
‡ Average of ten points stimulated three times each.

to invalidate such an assumption. At any rate, it is not understandable how an increase in the error of localization of 100 per cent or more could result from a slight spread in the stimulated area. This is particularly true because the warmth and pain spots were carefully selected and only those of particular sensitivity were chosen, so that the surrounding area was unquestionably less sensitive to the stimulus used. This leaves only one other possibility for explanation. It seems probable that, in spite of the fact that the sensation caused by tactile and that by nontactile stimulation of the same sense organ were nearly identical and that no touch sensation was noticeable, an element entered of which the subject was not conscious. This element must have resulted from the actual contact of the stimulator with the skin. It is reasonable to assume that the deformation of the skin resulting from this contact caused stimulation of pressor receptors. The excitatory processes which

followed this stimulation were responsible for the significant differences in the error of localization in tactile and in nontactile experiments. Thus, we come to the conclusion that stimulation of sense organs may have a definite physiologic effect (improvement in localization), although the corresponding touch sensation does not pass the level of consciousness because it is suppressed by the more intensive sensations elicited at the same time.

That stimulation of sense organs may have definite physiologic effects although no sensations may arise is also known from other observations. In the investigations of one of us (E. G.) and his associates [6] on spinal irradiation, it was found that the cutaneous localization of pain, touch and temperature spots was definitely altered several minutes after the pain which was elicited to produce the phenomenon of spinal irradiation had disappeared completely. Ebbecke [7] observed that after-images resulting from stimulation of the retina with an intense light disappeared by increasing temporarily the illumination in the room but that the sensations (after-images) may then reappear even after minutes, when the effects of the increased light adaptation have worn off. These and other observations show that the effect of stimulation of a sense organ is not dependent on consciousness of the sensation. Stimulation of the sense organ must have a physiologic effect as soon as the intensity of the stimulus has reached the threshold value. Such a stimulus, however, may or may not produce a conscious sensation; this is dependent on the excitatory processes which reach the cortex of the brain at the same time.

CONCLUSIONS

Tactile stimulation of cutaneous sense organs involving pain and warmth endings, respectively, leads to a lesser error in localization than does nontactile stimulation of the same sense organs. This seems to be due to the fact that the touch sense is involved in the tactile experiments, although no conscious touch sensation is elicited. The significance of this phenomenon is discussed.

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6. Gellhorn, E., and Northup, J.: Am. J. Physiol. **104**:537, 1933. Gellhorn, Gellhorn and Trainor.[4]

7. Ebbecke, U.: Arch. f. d. ges. Physiol. **221**:160, 1928; J. f. Psychol. u Neurol. **37**:72, 1928.

PREPSYCHOTIC PERSONALITY OF PATIENTS WITH AGITATED DEPRESSION

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The term agitated depression is widely, but not definitively, used. Its scope varies from interchangeability with involutional melancholia to application to youthful depressions with psychomotor unrest. An approach to the validity of the syndrome is a study of the prepsychotic personality of a group of patients falling within this category. If a uniform personality type is found, distinctive from the average, an attempt can be made to correlate or to contrast it with described prepsychotic personality types, in order thereby to establish more accurately the position which this group merits in any diagnostic classification.

Kraepelin first described agitated depression as one of six types of mixed states of the manic-depressive psychoses. The continued use of the term is an index to its clinical usefulness. Henderson and Gillespie [1] viewed it as the only entity in the group, considering the other types as transitional episodes between the manic and the depressive state. It is described as such an entity by modern textbooks and is included in the present system of classification. The Statistical Guide of the State of New York Department of Mental Hygiene (1934), conforming to the Standard Classified Nomenclature of Disease, states that agitated depression is the "most frequent of these" (mixed states) and describes it as "a depression of mood but with increased motor activity and at times pressure of thought."

In choosing cases for study, clinical criteria were first set up to make the study definitive. These features were: (1) depression without retardation; (2) psychomotor unrest, and (3) anxiety relating either to self or to environment, even at times merging into anxious delusions.

Six men and four women exhibiting these signs were chosen for evaluation of personality. The clinical data relating to the illness, findings and outcome are included in table 1.

The average age was 45.2 years, and the range, from 33 to 52. Nine of ten patients showed a distinct precipitating factor, three of six men exhibiting the reaction in response to actual or impending promotions, two to financial reverses and one to an unwanted pregnancy of his wife and difficulties at his

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From the Department of Psychiatry, Cornell University Medical College.

Read in part before the Section on Neurology and Psychiatry of the New York Academy of Medicine, April 14, 1936

1. Henderson, D. K., and Gillespie, R. D.: A Textbook of Psychiatry for Students and Practitioners, ed. 3, New York, Oxford University Press, 1932.

TABLE 1.—*Clinical Data on Ten Patients Suffering from Agitated Depression*

Case	1	2	3	4	5	6	7	8	9	10
Sex	M	M	M	M	M	M	F	F	F	F
Age, yr. (average 45.3)	33	52	42	46	44	52	43	42	47	51
Precipitating factor	Familial vocational	Financial	Impending promotion	Promotion	Promotion	Financial	.....	Vocational	Familial death	Personal illness
Duration before admission, mo	3	15	6	8	2	4	3	6	8	5
Prodromes										
Restlessness	++	+++	++	++	++	++	+++	++++	++++	++++
Insomnia	+++	++++	+++	+++	+++	++++	+++	++++	++++	+
Anorexia	+	++++	++++	+++	+	++	+	+++	+++	+
Anxiety	++	+++	++++	++++	+++	++++	+++	++++	++++	++++
Loss of weight	++	+++	+++	+++	++	+++	+	+++	++	—
Clinical findings										
Depression	++++	+++	+++	++	+++	+++	+++	++++	++++	++++
Restlessness and agitation	++	+++	++	+++	+++	+++	++++	++++	++++	+++
Tension	++++	++++	++	+++	++++	+++	++++	++++	++++	++++
Anxiety	++	++	++++	+++	+++	++++	+++	++++	++++	++++
Indecision	—	++++	+++	—	—	+++	—	—	+++	+++
Retardation	—	—	—	—	—	—	—	—	—	—
Somatic preoccupation	—	++++	++++	+++	—	+++	+++	+	—	++
Financial preoccupation	++	+++	+++	++++	+++	++++	—	—	—	+
Difficulty in concentration	+++	+++	++	++++	++	++	+	++	++	+++
Self-condemnation	++++	—	++	+++	+++	—	—	+++	+	++++
Suicidal threat	+	+	+	—	+	+	+	—	—	—
Suicidal attempt	++++	+	—	—	—	—	+	—	—	—
Time in hospital	5 mo.	4 mo.	3 mo.	4 mo.	12 days	2 mo.	1 mo.	4 mo.	4 mo.	6 mo.
Condition on discharge	Improved	Much improved	Much improved	Slightly improved	Unimproved	Improved	Unimproved	Recovered	Unimproved	Much improved

work. One woman responded to a threat to her position, another to a long illness and a third to the death of a relative in her home.

The depressions were present from two to fifteen months before admission to the hospital, during which all the patients exhibited psychomotor tension, varying from irritability and excessive worry to actual pacing the floor and wringing the hands. Insomnia was a presenting complaint in nine of ten cases. Anorexia was prominent in six and appeared in all. In all cases there were actual anxiety reactions, grading up to a fear response. Loss of weight was recorded in nine of ten cases and was significant (from 20 to 35 pounds [9.1 to 15.9 Kg.]) in eight.

Clinical study showed depression, extreme restlessness merging into agitation, tension and obvious anxiety reactions in all cases. Indecision was present in five instances. Retardation was absent in all. All the patients were preoccupied with somatic or/and financial complaints, except one woman, who, in an almost stereotype fashion, urged to "go home." All exhibited difficulty with concentration; six showed self-condemnatory trends; five spoke of suicide, and three made actual attempts. With therapy one patient was discharged as recovered, three as much improved and three as unimproved. The discharges with improvement occurred after a stay in the hospital of from two to six months, the average being four months.

A second group of five men and five women, of average intellectual endowment, were chosen as controls. An attempt was made not to include those with extremes of personality. None had suffered a frank nervous disorder. The range of ages was from 24 to 55, the average age being 39.5.

In a previous study [2] fifteen traits were used to determine the reaction pattern of persons in whom involutional melancholia had developed. The scope of these traits was closely defined at that time, and the same limits were set in this study. These traits are: interests, adjustability, sociability, friendliness, tolerance, sexual adjustment, ethical code, saving, reticence, sensitivity, anxiety, stubbornness, overconscientiousness and meticulosity regarding the person and the work.

The intensity with which each person exhibited each trait was evaluated and graded from — to + + + +. This grading was repeated independently after a period and a mean grading used whenever slight variation appeared, although there was actually little or no variation in the two estimations.

Data relative to the personality of each of the ten patients are given in the following section.

REPORT OF CASES

CASE 1.—A capable bookkeeper aged 33, an only child, was unduly attached to his father. During adolescence he mixed poorly and chose solitary amusements. As an adult he shunned social occasions and had no friends. Forced changes in his routine gave rise to an irritative reaction. Although attractive to women, he paid little heed to them until he courted his wife. After marriage, at the age of 27, sexual adjustment was a cause of worry, and his demands were always minimal. He was strongly opposed to the pregnancy of his wife, which precipitated the depressive reaction. Insistently stubborn and easily offended, he saw slights when they were not intended and could never take a joke. His employers valued his steadfast attention to duty. He was constantly subject to worry about the future and was always pessimistic. His personal appearance was a matter of great vanity to him.

2. Titley, W. B.: Prepsychotic Personality of Patients with Involutional Melancholia, Arch. Neurol. & Psychiat. **36**:19 (July) 1936.

CASE 2.—A man aged 52, a successful salseman in Central and South America until the economic depression, was the only son of an irascible, elderly father and an ambitious mother. He never displayed an interest not allied to the product he was selling at the moment, and he had no recreational outlets. A solitary drinker of moderate amounts, he cared nothing for social events, had no friends and insulted his wife's friends if they appeared while he was at home. He was completely intolerant of any view disagreeing with his concepts. He was never aggressive sexually and was continent during absences of weeks from his wife. He always exhibited complete impotence for a month before sailing on a trip. He had not wanted his daughter, an only child, was jealous of any attention his wife bestowed on her, expressed pleasure when she married and made no attempt to see her thereafter. He was extremely neat in his personal appearance and markedly fussy about his belongings. Every detail of his reports had to be attended to before he could relax in the least.

His ethical code had been established by his mother, and he never deviated from it. He was always frugal in his expenditures. Closemouthed at all times, he never expressed his feelings to his wife except when his extreme sensitivity to criticism was aroused or when his insistent stubbornness was called into play.

CASE 3.—A man aged 42, a deputy county comptroller, was always a model son to his parents. He visited them daily except for a short period when a superior position took him away from them, but he left this position rather than be separated from them. His childhood and adolescence were marred by severe and prolonged illnesses. His marriage to a widow with one son, of whom he was very fond, was successful, but he insisted that there be no children. He boasted of covering his real feelings from all but admitted to shrinking bashfulness and sensitivity. He was fairly malleable until crossed, when he became stubbornly argumentative. He demanded the same methodical attention to detail from his inferiors that he himself exhibited. The immaculate appearance of his home and person was a matter of great pride to him. While his work forced a wide acquaintanceship on him, he reduced his social activities to a minimum, even quarreling with his wife about the amount of socializing they should do, and consequently he had few friends. Behind a mask of worldliness, he was intolerant of any actions which violated his code of ethics and was always insistent that the "right thing" be done.

CASE 4.—A man aged 46, an executive dealing with university extension courses, as a child was dependent on his mother, suffered from enuresis and had several overt homosexual experiences. After his marriage, at the age of 28, he was irritable, dissatisfied and excessively jealous for several months. A diligent and conscientious worker, he had no hobbies, disliked any social activities and had no friends. He was suspicious of the motives of acquaintances and consequently felt slighted by them without cause. Throughout his married life he begrudged any attention his wife gave to others. He had no sense of humor, was intolerant of the views of others and was often irritable and faultfinding. He was economical to the point of parsimony, except when there was need of medical care for some member of the family, concerning whose health he was anxiously considerate. His wife learned of his extreme personal sensitivity from his reaction, which was retreat into hurt silence, rather than from any confidences, of which he was at all times reticent. While he was easily aroused sexually, he was not aggressive and had practiced intermittent masturbation since youth. In dress he was always immaculate.

CASE 5.—A man aged 44, a district commercial manager for a public utility, in childhood had presented nothing unusual except that he was always known as an exceptionally well behaved child. Known as an energetic, hard worker,

he had no recreational interests. While he was respected by his business colleagues, he had no friends. At the age of 19 he married a woman 4 years his senior, and from this union a daughter was born. He and his wife practiced continence to prevent further conceptions. His "code" placed the interests of his employers first, and he was critical of any one who did not do similarly. When there was any occurrence which disturbed the even tenor of his routine, he reacted in an irritable manner. He was stubborn in his convictions. Throughout life he was completely reticent as to his personal feelings on any subject, and nothing was known of his inner reactions.

CASE 6.—A man aged 52 left the managership of a bank at 34 to become a successful insurance broker. He had been considered a nervous infant. His mother died when he was 5 years old, and his father remarried twice; the patient disliked both stepmothers. His business and home bounded his interests completely, and he never took more than two weeks' vacation. He postponed marriage until he was 37 because he "couldn't afford it before." He was almost abstinent in his sexual demands, and his wife always took the initiative. His financial status was a matter of apprehension and concern to him, and he invested his savings only in a home and insurance. He never discussed his feelings with any one and was very quiet with his wife, refusing to argue but inexorably adhering to his own views on any subject. He was described as "prim" both in appearance and in business affairs.

CASE 7.—A woman aged 45, who had either held office positions or done light factory work, in childhood presented nothing unusual. From adolescence she had been a poor mixer, retiring and bashful, and had never been close to any one other than her mother; even with the mother she had retained a certain reticence, concealing for years a deep interest in Christian science. She was never able to adjust away from the home circle, although she tried the experiment several times; she always returned after a short interval. She never displayed interest in sex problems, either directly or indirectly, and never had any men friends. Even though she never made more than a modest wage, she lived frugally and managed to save money. Always retiring, she was known to her intimates as a very sensitive person. Her employers commented on her as a "reliable, trustworthy worker" who always showed "good sense."

CASE 8.—A woman aged 42, a housewife who combined each day a half-day's work as a court stenographer with rearing three children, had been a studious child; she preferred reading to mixing with other children and after finishing high school at the age of 16 taught herself shorthand and typing, at which she became expert. Her family, her work, which was an economic need, and church work were the limits of her interests. She held her many acquaintances at arm's length and made no real friends. Little is known of her sex life except that she fled from the advances of a man of whom she was very fond before her marriage and wanted only one child. She was deeply religious and was guided by a strong code of right and wrong, from which she condoned no deviation in herself or in others. While extremely sensitive and easily hurt, she was so reticent that this was not generally known. Positive, opinionated and argumentative in her views, she could not brook opposition. She worried constantly about the economic status of her family; her ne'er-do-well husband offered some justification for this attitude. Her ability to appear neatly dressed and have her children well clothed in her straitened circumstances was a matter of comment among her acquaintances. Her home was kept spotlessly clean, and any disarray caused her anguish.

CASE 9.—A woman aged 47, a housewife who limited herself completely to her home, had become an orphan in early childhood and was raised by two aunts and a bachelor uncle, who were strictly Victorian in their attitudes. She disliked and refused to enter any form of social activity or show any interest in those available to her through her husband's prominence in various organizations. She had no friends during any period of her life and maintained a rigid reserve, even with her husband. Throughout marriage she resented marital relations, was frigid and insisted that there be no children. Ordinarily placid, she gave the impression of being bored when with people. She became uncomfortable and anxious about speeding in an automobile or when there was any discussion of illness or death. Meticulous about her home and person, she kept a perfect household. During her married life she was an indefatigable shopper and spent untold amounts of energy to save a few cents, even when there was no great necessity for it. No amount of dissuasion by her husband could change her quietly stubborn attitude regarding the details of her life.

CASE 10.—A woman aged 51, an unmarried school teacher, the second of four children, was considered a delicate child. She suffered from hyperthyroidism at intervals until she underwent operation, at the age of 35. She lacked ambition to be other than a grade school teacher, but appeared happy in that rôle. Shy, timid and retiring, she shunned social activities, having a limited coterie of superficial women acquaintances of her own category. She was tremendously attached to her mother, yet reticent with her. She was prudish and never displayed the least interest in men. At the age of 45 she became fond of an older man, but refused to marry him because he would have needed her support. She was oversolicitous regarding her health and consulted physicians frequently. Her strong sense of duty and extreme conscientiousness in all activities were emphasized.

Estimations of the personality responses are shown in table 2. Narrow interests, difficulty in adjustability, lack of sociability and friendliness and intolerance are almost constantly present. Sexual adjustment is almost universally poor. A rigid ethical code is a positive factor; propensity for saving is always present, and a deep tone of anxiety is prominent. Stubbornness is always notable, and overconscientiousness is pronounced. Fussy meticulosity, as to both work and person, is present to an exaggerated degree.

As is particularly notable in this chart, the ensemble of traits which make up the personality picture is similar in all cases, despite minor variations from person to person. These deviations might well be expected in a group with such a wide variation in background and occupation, without changing the basic motif.

The data on the ten average personalities are shown in the same fashion in table 3. While there are more frequent and greater variations in individual persons, the total effect is much different. The general uniformity, despite isolated individual variations, is noteworthy as a normal pattern so far as these traits are concerned.

Breadth and variability characterize the interests of these persons. Adjustments are made without effort. Sociability and friendliness are constant, and tolerance is a noteworthy trait. Sexual adjustment is

TABLE 2.—*Estimation of Personality Traits in Ten Patients with Agitated Depression*

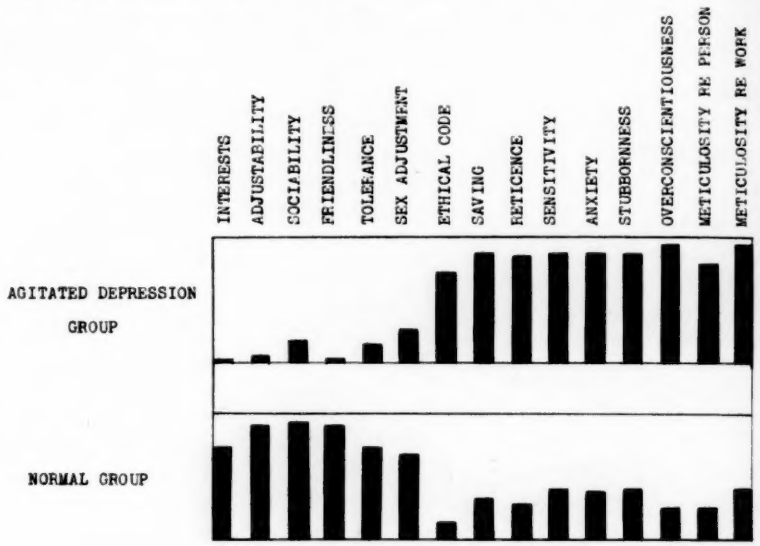
Case	1	2	3	4	5	6	7	8	9	10
Sex	M	M	M	M	M	M	F	F	F	F
Age, yr	33	52	42	46	44	52	43	42	47	51
Interests	+	−	−	−	−	−	−	−	−	−
Adjustability	−	−	−	−	+	−	+	−	−	−
Sociability	−	−	++	−	+	+	+	++	−	−
Friendliness	−	−	+	−	−	−	−	−	−	−
Tolerance	+	−	+	+	+	−	+	−	+	−
Sexual adjustment	+	−	++	++	++	+	−	+++	−	−
Ethical code	++	++	++++	+++	+++	+++	+++	++++	++	+++
Saving	+++	+++	+++	+++	++++	++++	+++	++++	++++	++++
Reticence	+++	++++	+++	++	++++	+++	++++	++++	++++	+++
Sensitivity	+++	++++	++++	++++	++++	++	++++	++++	+++	+++
Anxiety	++++	+++	+++	++++	+++	+++	++++	+++	++++	++++
Stubbornness	++++	++++	++++	++++	++++	++	++	+++	++++	++++
Overconscientiousness	++++	++	++++	++++	++++	++++	++++	++++	++++	++++
Meticulosity (re person)	+++	+++	++++	+++	+++	+++	++	+++	++++	+++
Meticulosity (re work)	+++	++++	++++	++++	++++	++++	+++	++++	++++	++++

TABLE 3.—*Estimation of Traits in Ten Persons with Average Personalities*

Case	1	2	3	4	5	6	7	8	9	10
Sex	M	M	M	M	M	F	F	F	F	F
Age, yr	46	39	55	46	40	42	31	24	30	38
Interests	++	+++	++	++	++	++++	+++	++++	+++	++++
Adjustability	+++	++++	++++	+++	+++	++++	++++	++++	++++	+++
Sociability	++++	++++	++++	++++	++++	++++	++++	++	+++	++++
Friendliness	+++	++	++++	++++	++++	++++	++++	+++	++++	++++
Tolerance	+++	+	+++	++++	+++	+++	++++	++	++++	++
Sexual adjustment	+++	+++	++++	++++	+++	++	++	+	+++	++
Ethical code	−	−	−	−	−	+	++	+	−	+
Saving	+++	−	+	−	+	++	++	−	−	++
Reticence	++	−	++	+	−	−	+	++	++	+
Sensitivity	+	++	−	+	++	++	++	++	++	++
Anxiety	++	++	−	+	++	++	−	++	+	++
Stubbornness	+	++	+	++	+++	++	+	+	+	+++
Overconscientiousness	++	−	−	−	++	+	++	−	+	++
Meticulosity (re person)	+++	−	−	++	++	+	−	−	−	++
Meticulosity (re work)	+++	+	+	−	+++	++	+	+	++	++

more adequate. Propensity for saving is a minor motif or absent. Reticence is not pronounced; sensitivity, even when present, does not dominate the personality, and anxiety does not play a major rôle. Stubbornness, when present, is not unyielding. Conscientiousness is not exaggerated. The person is not subject to fastidious care, and work is accomplished without strained and painful attention to detail.

If the pluses for each trait in each person are summated and plotted as vertical bars, the juxtaposition of the intensities of the traits and thereby the contrast between the group of patients under study and the normal group are more clearly visualized.



Graph showing intensity of traits for ten normal persons and ten patients with agitated depression.

A composite picture of the personality in cases of agitated depression may now be drawn. The scope is generally limited to the home or/and work, with occasional admission of the church.

During childhood the person is shy, timid and retiring and is accounted a model for others. Adolescence finds him continuing in the same vein and little interested in the usual pursuits of that age, generally preferring more serious interests, of an adult nature. Already a propensity for championing the "proper" course or the "right thing" is apparent. Except when his code is threatened, however, he is reticent and does not reveal any special depth of feeling, even though his associates begin to recognize sensitivity of a type not aroused by or susceptible to gibes. If late adolescence finds him in college, he adjusts to

this major change in environment with great difficulty, and often with much anxiety.

The end of schooling finds him a worker whom employers appreciate. Earnest, prompt, diligent, unvaryingly honest and dependably exact, he is as frugal with his employer's time and money as with his own. Marriage tends to be delayed on various pretenses and is entered into in a spirit of conformity to expected behavior rather than in response to any great emotional urge. Children are avoided on one pretext or another, or if these excuses fail their arrival gives rise to anxious forebodings. No emotional bonds are established between him and his marital partner or children, but respect is demanded; their conduct is dictated by his code and rigidly, without allowance for human frailty.

Middle age finds him a respected, and at times feared, but little loved member of his home and community. In business he is valued by his superiors because of his assiduity, though at times his stubborn adherence to established custom is exasperating even to them. His subordinates, though bound to admire his tenets, are held in awe by his lack of humor and the firm manner in which he holds them to detail. The commonly accepted recreations are foreign to him. If any concession is made in this sphere it is indulged in a businesslike fashion and without any sense of play. Personal finances are a matter for hesitant caution, and only the most conservative investments are made. This propensity is carried to the extremes of frugality, and even to penury. Friendships are conspicuous by their absence, or are generally limited to a few, who must accept his reticence, taciturnity and frugality if they are to be so rated. His health, or that of his family in certain instances, is a matter for some preoccupation. The respect of the community is his, but no man feels that he knows him. His existence is so subject to routine that it is often facetiously said that clocks can be set by the punctuality with which he does things.

The feminine counterpart is even more narrow in her views, but is likewise capable in her sphere. Any disarray in her home is upsetting. Everything is performed in a meticulous and inflexible manner, and any deviation arouses anxiety. Marriage is a matter of convenience, and little emotion enters the pact. Frigidity, often accompanied by actual distaste for sexual union, is the rule. While her ability as manager of her home is acknowledged, all who come in contact with her recognize her aloofness.

Combination of these factors of personality with superior intelligence results usually in material achievement above the average. The person of low average intelligence, however, will be found filling a drudgelike position, having minutiae as his great responsibility and reassuring himself with the thought that he is indispensable because of his exactness, wherein he is most pedantic.

COMMENT

The scope of this problem has been limited to the objective aspects of the personality. The psychologic or/and the physiologic or, to use Adolf Meyer's term, the psychobiologic factors, be they causative or contributory, are a matter for further study.

In a previous study [2] it was shown that the same pattern appears in the prepsychotic personality of the patient with involutional melancholia. It was also shown that it is in strong contrast to the prepsychotic personality of the person who experiences a manic-depressive depression. These facts, coupled with the many similarities in the clinical picture of agitated depression and that of involutional melancholia, particularly the practically identical prodromes, point to a basic relationship between them. It would also seem to be indicated that agitated depression should be differentiated from the manic-depressive psychoses in systems of classification and be correlated more closely with involutional melancholia. Studies attempting to clarify this relationship are in progress.

SUMMARY AND CONCLUSION

Ten patients with depressions in middle life, showing particularly depression without retardation, psychomotor unrest and anxiety, were studied with reference to the prepsychotic personality. The intensity with which each patient exhibited a group of personality traits was evaluated. A constant reaction pattern was demonstrated. Narrow interests, difficulty in making adjustments to change, asocial and unfriendly attitudes, intolerance and poor sexual adjustment appeared constantly. A rigid ethical code, proclivity for saving and extreme reticence, coupled with markedly sensitive and anxious trends, recurred throughout. Stubbornness, overconscientiousness and meticulosity as to person and vocation were notable.

Ten average personalities evaluated in the same manner presented a strongly contrasting picture in each trait estimated, but most notably as far as the total personality was concerned.

On the basis of this study, the prepsychotic personality of the patients with agitated depression is identical with that of persons in whom involutional melancholia develops, and is quite distinct from the average personality or the prepsychotic personality of persons who have clearcut manic-depressive depressions.

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FAMILIAL NEUROSYPHILIS OF THE DEMENTIA PARALYTICA TYPE

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The term "familial neurosyphilis" is usually used to denote involvement of the central nervous system by syphilis in two or more members of the same family. The existence of this situation has been reported repeatedly because it presents the problem of explaining the occurrence of the same type of syphilis in two or more members of the same family. Despite the fact that a great many clinical observations and much experimental work have been carried out, no adequate explanation is as yet forthcoming. The two theoretical explanations to be considered concern, first, the nature of the infective organism with regard to its specificity and virulence and, second, consideration of the person infected with regard to a possible specific familial predisposition to this type of infection.

In this paper it is our purpose to add further clinical observations relative to the occurrence of neurosyphilis in two or more members of the same family, in the belief that at some future time sufficient clinical evidence combined with experimental work will solve this important problem.

CLINICAL OBSERVATIONS

Family History in Juvenile Dementia Paralytica.—In a study which one of us (W. C. M.) made of 46 cases of juvenile dementia paralytica in which the patients were examined personally and of 610 cases reported in the literature,[1] it was possible to obtain definite information about the family history in 402 cases. In 146 of these cases (36.3 per cent) there was clinical evidence of neurosyphilis in one or more of the other members of the family. This high percentage is even more significant when one considers that this series did not include cases of asymptomatic neurosyphilis in other members of the family; both clinical and serologic evidences of the disease were shown. The average incidence of clinical neurosyphilis is from about 10 to 15 per cent of all types of

Read at a meeting of the Missouri-Kansas Neuropsychiatric Society, Kansas City, Oct. 28, 1936.

1. Menninger, W. C.: Juvenile Paresis, Menninger Clinic Monograph Series, no. 1, Baltimore, Williams & Wilkins Company, 1936.

syphilis, which, when compared with 36.3 per cent in the families of the patients with juvenile dementia paralytica, is strong evidence for the theory that a special factor operates in neurosyphilis.

Dementia paralytica represents less than 5 per cent of all types of late syphilis, according to Turner's [2] figures. In 7 per cent of a series of 400 cases of unquestionable neurosyphilis studied by Kemp and Menninger [3] dementia paralytica was found. In contrast to these low percentages, in the present series of cases dementia paralytica was present in 14.7 per cent of all cases of neurosyphilis in other members of the family.

In addition to these figures, one of us (M. G.) has had the opportunity to examine 57 patients with dementia paralytica in the University of Berlin clinic for neurology and psychiatry during the last ten years.[4] Again, in many instances the parents could not be examined, since some of the children came from an orphan asylum. Nevertheless, in 15 of this series of 57 cases neurosyphilis was present in one parent, and in 3 instances there was clinical evidence of neurosyphilis in both parents. Thus, these figures substantiate the findings in the large series collected from the literature, namely, that the incidence of neurosyphilis is from two to three times as great in the parents of patients with juvenile dementia paralytica as in the population at large. In the Berlin series dementia paralytica was the most frequent clinical type of neurosyphilis in the parents, and cerebral syphilis was the next most common form.

These findings conclusively contradict the observations of Dennie,[5] who, though recognizing that the children of tabetic patients often have neurosyphilis, stated that parents with dementia paralytica nearly always beget children free from involvement of the central nervous system.

Occurrence of Neurosyphilis in Both Parents and in Offspring.—Spectacular illustrations of the occurrence of parental and juvenile dementia paralytica in the same family are furnished by the 6 cases recorded in which both parents had dementia paralytica and a child showed the juvenile form. These cases were reported by Major (1892),[6]

2. Turner, T. B.: The Race and Sex Distribution of the Lesions of Syphilis in 10,000 Cases, Bull. Johns Hopkins Hosp. **46**:159-184, 1930.

3. Menninger W. C., and Kemp, J. E.: The Incidence of the Clinical Types of Neurosyphilis in Males, in Pregnant, and in Non-Pregnant Females, J. Nerv. & Ment. Dis. **83**:275-280 (March) 1936.

4. Grotjahn, M.: Zur Klinik und Psychologie der juvenilen Paralyse, Monatschr. f. Psychiat. u. Neurol. **92**:299-315 (Feb.) 1936; **93**:19-33 (March) 1936.

5. Dennie, C. C.: Familial Neurosyphilis, J. A. M. A. **95**:1571-1576 (Nov. 22) 1930.

6. For other references see bibliography of Menninger.[1]

McDowell (1908), Baudouin and Lévy-Valensi (1910), Sträussler (1910), Lafora (1913) and Menninger (1930). Menninger's case has previously been reported.

In addition to the instances recorded in which both parents had dementia paralytica, 7 cases are reported in the literature in which both parents had neurosyphilis. Apert and his associates (1907)[6] reported the case of a 15 year old girl who questionably acquired syphilis from her parents after birth, the mother having tabes and the father dementia paralytica. Kleineberger (1908) [6] reported 2 cases, one of a girl aged 10, and the other of a woman aged 21, in both of which the mother had tabes and the father dementia paralytica. Halben (1909) [6] reported the case of a 10 year old girl with juvenile tabes and dementia paralytica whose mother had tabes and whose father had dementia paralytica. Southard and Solomon (1917) [6] described the case of a boy aged 15 whose mother and father both presented clinical evidence of neurosyphilis. Klauder and Solomon (1923) [6] reported the case of a girl aged 12 whose mother had cerebral syphilis and whose father had dementia paralytica. Marie (1926) [6] reported the case of a youth aged 18 years whose mother had cerebral syphilis and whose father had dementia paralytica.

In addition to these instances in which both parents had neurosyphilis and the offspring juvenile dementia paralytica, we report briefly the histories in 2 additional cases observed by one of us (M. G.) and not previously reported in which both parents had neurosyphilis.

REPORT OF CASES

CASE 1.—The patient was a woman aged 22 at the time of examination. The father died at the age of 45, two days after admission to the psychiatric division of a general hospital, in a state of acute confusion and disorientation. Physical and laboratory examinations were not made, but postmortem examination disclosed syphilitic aortitis, cerebrovascular syphilis and atrophy of the liver. The mother, at the age of 46, experienced two cerebrovascular accidents, with hemiparesis on the right side and aphasia. Under intensive medication with potassium iodide she improved. At the age of 56, when she brought her daughter for examination, she presented contracted, unequal, fixed pupils, diminished abdominal reflexes on the left and a Babinski sign on the right. The deep reflexes were increased on the right, but there was no paresis or aphasia. Mentally, she was depressed, worried about her undeserved illness, had a strong feeling of guilt about her daughter's illness and was emotionally unstable. The Wassermann reactions of the blood and spinal fluid were strongly positive, with an increase in cells in the spinal fluid and a syphilitic colloidal gold curve. During the next three years, with fever treatment, the cerebrospinal syphilis did not progress. A son born to a previous marriage was healthy.

The daughter had developed normally until the age of 13 years. At that time her character changed; she did poor school work, became disorderly and uncleanly and was irritable and forgetful.

Neurologic Examination.—The pupils were dilated, fixed and unequal. There were: disturbance in speech, absence of knee and ankle reflexes and ataxia of all extremities, particularly the lower. The mental state was one of hyperactivity and euphoria, with loquaciousness and irritability, and there was difficulty in concentrating.

Laboratory Examinations.—The Wassermann reactions of the blood and spinal fluid were strongly positive, with a marked cellular reaction of the spinal fluid.

Course.—After examination in 1928, a course of malaria was given, after which 3 Gm. of neoarsphenamine was administered; dermatitis developed at this point. Although there was no further treatment, the patient appeared well when reexamined in 1935, had married and been divorced and had again become engaged. The neurologic findings were unchanged, but six examinations of the spinal fluid during the interval of seven years had all shown improvement, with normal results. The patient had one daughter, aged 5 years, born two years after the malaria treatment, who was a bright, lively, well developed child, with negative serologic reactions and no evidence of congenital syphilis.

Case 2.—The patient was a youth aged 17. The father, aged 55, for thirty years had had extensive treatment with neoarsphenamine, bismuth and potassium iodide. The Wassermann reactions of the blood fluctuated from positive to negative. Examination revealed fixed, contracted pupils and absence of knee and ankle jerks, but no mental disturbance. The mother, aged 53, had had three miscarriages and came for examination two years after her son had been found to have juvenile dementia paralytica. For six months she had had severe headaches. Neurologically, she presented unequal pupils, which reacted poorly to light and in accommodation. The deep reflexes were increased on the right, and a Babinski sign was present on this side. She showed slight intellectual deterioration and some emotional instability. The Wassermann, Kahn and Meinicke reactions of the blood and spinal fluid were positive; there were 12 cells per cubic millimeter of spinal fluid. She was given fever treatments and, when reexamined eight months later, showed slight improvement, though the Wassermann reaction of the spinal fluid remained strongly positive, with 4 cells per cubic millimeter.

The son had shown retarded mental development since birth. He had never learned to read or write and was unable to go to school. At the age of 15 years he had the first convulsion; with the administration of phenobarbital, no further convulsions occurred in the next year and a half. They then reappeared and were the cause of hospitalization.

Neurologic Examination.—The pupils were dilated and unequal and reacted poorly to light. The deep reflexes were increased. The lad presented a picture of marked feeblemindedness and was mute and untidy.

Laboratory Findings.—The Wassermann reactions of the blood and spinal fluid were strongly positive.

Course.—A course of malaria was given, but about one year after examination the patient died in the course of a series of severe convulsions.

Occurrence of Juvenile Dementia Paralytica in Two Offspring.—Even more spectacular than the occurrence of neurosyphilis in both parents and in the offspring is that of neurosyphilis in two or more members of the same family. One of us (M. G.) examined two siblings with juvenile dementia paralytica whose father had dementia paralytica and whose mother had cerebrospinal syphilis.

CASE 3 and 4.—The patients were a girl aged 5 and a man aged 21 years. The father, aged 45, when bringing the second child for examination, presented the neurologic findings of unequal, fixed pupils, disturbance in speech and increased deep reflexes. Mentally, he showed emotional instability, disturbance in memory and intellectual enfeeblement. Laboratory data were not available, but the diagnosis was conclusively that of dementia paralytica. The mother had died at the age of 38, of a sudden apoplectic stroke on the left side. The diagnosis of cerebrovascular syphilis was made. The first sibling, a daughter born Feb. 19, 1909, was unable to walk or speak at 2 years of age and never progressed. She had many convulsions. She presented idiotic, infantile behavior, and the Wassermann reactions of the blood and spinal fluid were positive. She died at the age of 5 years, of pneumonia. Postmortem examination showed dementia paralytica. The second sibling, a son born July 20, 1910, was retarded in physical development and could not make progress intellectually, even in an institution for the feebleminded. He was able to adjust by working with his father on a farm, with continuous close supervision. He came for examination at the age of 21.

Neurologic Examination.—The pupils were dilated and fixed. There was disturbance in speech, and the deep reflexes were increased. The patient was feebleminded to a moderate degree and showed an emotional tone of euphoria.

Laboratory Examinations.—The Wassermann reactions of both the blood and the spinal fluid were positive, with a marked increase in cells and curves characteristic of dementia paralytica in both the colloidal gold and the mastic tests.

Course.—Malarial treatments were given, with ten chills, followed by injections of neoarsphenamine. The man improved sufficiently to carry on his service in the *Arbeitsdienst* and received a certificate of good conduct.

Comment.—A third child was born in this family in 1923; when examined at 11 years of age, in 1934, he gave the impression of being feebleminded but showed no stigmas or clinical or laboratory evidence of neurosyphilis. The spinal fluid, however, was not examined. He remained in the first grade at school for three years.

Reports of 13 other cases in the literature in which two children in the same family had juvenile dementia paralytica were made by Hoch,[6] in 1892; Jouschenke, in 1896; von Speyr, in 1899 (the mother was tabetic); Sollier, in 1910; Trapet, in 1910; Huguet, in 1913; Kren, in 1915; Müller-Hess, in 1919 (the mother had tabes); Grütter, in 1920; Long-Landry, in 1921 (the father was tabetic, and two other children had neurosyphilis); Klauder and Solomon, in 1923; Menninger, in 1930, and Potter, in 1931.

Three Siblings with Neurosyphilis.—There are several reports of three or more members of the same family with neurosyphilis. One of these concerns a spectacular case described by Dennie,[5] in which the father had tabes and the mother apparently had latent late syphilis (not neurosyphilis); all six children showed a positive Wassermann reaction of the spinal fluid and evidence sufficient for a diagnosis of cerebrospinal syphilis. Duncan[7] reported a case in which three of

7. Duncan, A. G.: Familial Neuro-Syphilis with Apparently Healthy Parents, Lancet **1**:179 (Jan. 23) 1926.

six children had symptoms of neurosyphilis, although the parents gave neither a history nor signs of the disease. Homén (1890) [8] reported the unusual observation of three sisters, aged 12, 20 and 21 years, with dementia paralytica, on all of whom autopsy was performed. The histories were remarkably similar: In one case the duration of the illness was three years, in the second six years and the third seven years; in each instance there developed typical neurologic signs of dementia paralytica, marked regression and mental deterioration and, finally, contractures; at postmortem examination the classic observations of juvenile dementia paralytica were made.

Kingery (1921) [9] reported an instance of three children in the same family all of whom showed juvenile dementia paralytica. The father presented latent late syphilis, and the mother, only general adenitis and a strongly positive Wassermann reaction of the blood serum. The children were: a boy aged 8, who, though he improved somewhat after treatment, died of a convulsive attack; a girl aged 4, who had convulsions, loss of ability to speak, unstable emotional reactions and slight ataxia but who improved under treatment, and a boy aged 2, who, on the basis of laboratory findings, was given treatment before the appearance of symptoms. Later, however, he showed symptoms similar to those of his brother and sister, sufficient for a clinical diagnosis. This was substantiated by laboratory findings.

CASES 5, 6, 7 and 8.—The following family was seen in the Menninger clinic for the first time in 1930. The father and mother, who were peasant folk, presented no clinical evidence of syphilis; both had negative Wassermann reactions of the blood but gave a history of having been treated for syphilis. The mother's first pregnancy had resulted in a miscarriage. The paternal grandmother had been treated in the clinic for diabetes three years previously and gave a history of having had a positive Wassermann reaction of the blood. The family at this time (1930) consisted of three boys, aged 7, 5 and 3 years, respectively.

The oldest boy had been sickly as a baby; he ate poorly and was treated for rickets for about a year. He never walked alone, and his vocabulary did not exceed fifty words. In his third year he began to sit around doing nothing; at this time it was first noted that his pupils were unequal; he was taken to a physician, who treated him for "thyroid trouble." Convulsions began in his fourth year, and in his fifth year the spinal fluid gave a positive Wassermann reaction. Examination at the clinic showed: marked hydrocephalus; pes cavus; advanced choroiditis; bilateral atrophy of the optic nerve; fixed, unequal pupils; apparent deafness; a Babinski sign bilaterally, and Hutchinson's teeth. The Wassermann reaction of the blood was positive, but the spinal fluid could not be examined. When the parents were interviewed in October 1936, they reported that the child had died in February

8. Homén, E. A.: Eine eigenthümliche Familienkrankheit, unter der Form einer progressiven Dementia mit besonderem anatomischen Befund, Neurol. Centralbl. **9**:514-518, 1891.

9. Kingery, L. B.: A Study of the Spinal Fluid in Fifty-Two Cases of Congenital Syphilis, J. A. M. A. **76**:12-13 (Jan. 1) 1921.

1935, at the age of 13 years. He had grown steadily weaker and had never again been able to be on his feet; gradually contractures had developed; he had occasional convulsions and died of an intercurrent infection.

Between the first contact with the clinic in 1930 and the consultation in October 1936, neither parent had had any antisyphilitic treatment except that the mother received a few intramuscular injections during the period of a pregnancy in 1931. On examination in October 1936, the mother presented no abnormal physical findings, but the father showed sluggish, unequal pupils and hyperactive deep reflexes. The Wassermann reactions of the mother's blood were: Kahn antigen 1 plus, alcoholic antigen negative and cholesterolized antigen 1 plus; those of the father's blood were: Kahn antigen 1 plus, alcoholic antigen negative and cholesterolized antigen 1 plus. Investigation of the spinal fluid was impossible, but from the clinical examination it was assumed that the father had neurosyphilis.

The second child, a boy aged 5 years when seen in 1930, had a history of having been in good health until the age of 4 months, when "stomach trouble" developed. He walked at 13 months and talked at 15 months of age and seemed to develop normally. At the age of 5 years he became sulky, refused to obey and was irritable, abusive and much less talkative than formerly. When examined at this time, he presented unequal and nearly fixed pupils, used pronounced baby talk and showed inability to respond to the simplest command. He also had hyperactive deep reflexes and a positive Wassermann reaction of the blood. When examined in October 1936, at the age of 11 11/12 years, he gave an intervening history of never having gone to school. His vocabulary had increased markedly, however, so that he could swear and talk in a jumbled fashion, though with a noticeable defect in speech. The mother stated that he had not been able to take care of himself, his toilet or his dressing until he was 9 years of age. There developed a severe pulmonary infection, which progressed to an abscess of the lung and necessitated operative drainage. He was acutely sick with fever and for ten weeks was in a hospital, simultaneously receiving intensive antisyphilitic treatment. After the illness the family noticed that he improved markedly. He gained in weight; his vocabulary increased; he became able to attend to his own needs, and grew noticeably. On examination in October 1936 he presented a picture of somewhat retarded physical growth, adenoid, stupid-appearing facies, with the left pupil slightly larger than the right and responding poorly to light, a noticeably ataxic gait with broad-base, and hyperactive deep reflexes. Mentally, he was unable to carry on a simple conversation, though he made many spontaneous, irrelevant remarks. The Wassermann reaction of the blood was: Kahn antigen 2 plus, alcoholic antigen 2 plus and cholesterolized antigen 4 plus.

The third child, a boy aged 3½ years when examined in 1930, had a history of sitting up at the age of 6 months and walking at the age of 17 months; his legs, however, had seemed weak, and he resorted chiefly to crawling. He developed physically and seemed well until 3 years of age, when an infection of the scrotum developed from a splinter. After this the left ankle and left knee became swollen. On examination at that time he presented pupils that were nearly fixed to light, hyperactive deep reflexes and marked hydrocephalus. On examination in October 1936, at the age of 10, he presented an entirely different picture in that he apparently had developed normally, both physically and mentally. He had attended school regularly, was in the fourth grade and had done well in his studies. His parents noticed that he was somewhat nervous at times, and his teacher had remarked that his vision seemed poor. Physical examination disclosed only slightly unequal pupils, which responded promptly to light. The

deep reflexes were moderately hyperactive, and there was questionable slight diminution of visual acuity on rough testing. No other evidence of neurosyphilis was noted. The Wassermann reaction of the blood was 4 plus with all antigens.

A fourth child, a girl now aged 5 3/12 years had a normal birth; she weighed 10½ pounds (4.75 Kg.) and developed normally, walking at about the ninth or tenth month and talking soon afterward. At the age of 1 year the parents took her to a reputable hospital, for a Wassermann test of the blood; the result was reported to them as negative. The child presented an alert appearance and approximately a normal mental picture. Examination revealed a very large head, with prominent frontal bosses, possibly hydrocephalic, and a sluggish pupillary response to light; other than these findings there were no physical abnormalities or stigmas. The Wassermann reaction of the blood was negative with all antigens.

In this family the paternal grandmother had syphilis. The father presented clinical evidence of neurosyphilis; the oldest two children, typical pictures of juvenile dementia paralytica; the third child, suggestive signs of involvement of the central nervous system without symptoms, and a fourth child, one common stigma of congenital syphilis, without other signs or symptoms.

The clinical observations summarized here include those in 146 cases of juvenile dementia paralytica in which one or more additional members of the family had dementia paralytica; in 14.7 per cent of the cases of neurosyphilis occurring in these families the disease was dementia paralytica. We have collected 6 instances in which both parents and the offspring had dementia paralytica and 7 instances in the literature in which both parents had neurosyphilis. We have added 2 cases in which both parents had neurosyphilis and a sibling had juvenile dementia paralytica. In addition, we have cited several instances from the literature and 1 of a family observed personally in which several of the siblings had neurosyphilis.

NEUROTROPIC STRAIN OF SPIROCHAETA PALLIDA

The experimental evidence for a neurotropic strain is well summarized by Moore [10] in the statement that the problem is not solved. He reviewed the unconfirmed work of Reasoner [10] with a strain of spirochetes particularly likely to produce chorioretinitis in rabbits. The work of Levaditi and Marie [10] on differentiation of neurotropic and dermotropic strains has been specifically questioned by Jahnel,[10] who expressed the belief that they confused their neurotropic strain with Treponema cuniculi, the organism of spontaneous spirochetosis in rabbits. The unconfirmed work of Plaut and Mulzer [10] with a strain which causes rabbits to show pleocytosis in a high proportion of instances was uncontrolled with regard to the confusing factor of spontaneous encephalitis in rabbits.

10. Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933, pp. 36-37.

The clinical evidence presented here in the many instances in which two or more members of the same family had neurosyphilis lends strong clinical support to the existence of a neurotropic strain of Spirochaeta pallida. The older studies on the occurrence of neurosyphilis in the descendants of parents with dementia paralytica (Marie,[6] Junius and Arndt, von Rohden, Plaut and Goering, Semper, Wahl and Bonneau) strongly suggested such a strain of spirochetes. Likewise, various studies on conjugal neurosyphilis, particularly those of Junius and Arndt,[11] Schacherl,[12] Raven,[13] Seelert [14] and Moore and Kemp,[15] have supported such a hypothesis. Our present approach, namely, a study of the incidence of neurosyphilis among the parents of patients with juvenile dementia paralytica, was used by Kemp and Poole [16] in the study of neurosyphilis in parents of congenitally syphilitic children. They found that neurosyphilis is eight times as frequent among the mothers and three times as frequent among the fathers of patients in the neurosyphilic group. A similar method was used by Curtius and Schlotter,[17] who examined 10 families with juvenile tabes and found the same high incidence of neurosyphilis in the parents that is shown in our series of families with dementia paralytica.

FAMILIAL PREDISPOSITION

All the evidence which has been presented as suggesting a special strain of spirochetes could perhaps be equally well applied to the theory of a familial predisposition to neurosyphilis. One must recognize, however, that the term "predisposition" is merely a cliché, having no specific significance. It is a convenient term to explain a vague concept, without any direct reference to whether it is an inherent quality of the germ plasm—a specific attraction in particular types of the nervous system—and includes no suggestion as to what is meant in terms of heredity, anatomy or chemistry.

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11. Junius, P., and Arndt, M.: Ueber die Deszendenz der Paralytiker, Ztschr. f. d. ges. Neurol. u. Psychiat. **17**:303-401, 1913.

12. Schacherl, M.: Ueber Luetikerfamilien, Jahrb. f. Psychiat. u. Neurol. **36**: 521-549, 1914.

13. Raven, W.: Serologische und klinische Untersuchungen bei Syphilitikerfamilien, Deutsche Ztschr. f. Nervenh. **51**:342-401, 1914.

14. Seelert, H.: Untersuchungen der Familienangehörigen von Paralytikern und Tabikern auf Syphilis, Monatschr. f. Psychiat. u. Neurol. **41**:329-338, 1917.

15. Moore, J. D., and Kemp, J. E.: Studies in Familial Neurosyphilis: III. Conjugal Neurosyphilis, Arch. Int. Med. **32**:464-482 (Sept.) 1923.

16. Kemp, J. E., and Poole, A. K.: Familial Neurosyphilis: IV. Incidence of Neurosyphilis Among Parents of Congenitally Neurosyphilitic Children, J. A. M. A. **84**:1395-1398 (May 9) 1925.

17. Curtius, F., and Schlotter, H.: Zur Klinik und Erbbiologie der Juvenilen Tabes, Deutsche Ztschr. f. Nervenh. **134**:44-72, 1934.

An objection to the theory can be raised in the fact that the disease has frequently been known to die out in the same family, suggesting a change in the virulence of the organism rather than any conception of a strengthening or resisting influence of the nervous system. In the family we have just cited it is clear that the severity of the illness decreased in each succeeding child, and the most logical explanation is that the virulence of the organism decreases and in no way is concerned with the inherent qualities of the nervous system of members of the family. A further objection to the theory of predisposition is the fact that the children of neurosyphilitic parents who have had adequate treatment rarely have any form of syphilis.

The amount of clinical material which argues against the theory of a neurotropic strain and supports that of predisposition to familial neurosyphilis is meager. In 1907 Strohmayer [18] reported development of tabes dorsalis in two sisters, apparently from different sources. Burrow [19] in 1920 reported on a family in which there were 4 verified cases of tabes and an additional probable case, all the patients having acquired syphilis from a different source. Moore and Keidel [20] reported on 3 families, 2 of which contained 3 members each and the other 2 members, all of whom acquired syphilis from different sources and at different dates, yet neurosyphilis developed in all. This occurrence, they thought, was best explained on the basis of familial predisposition. Stewart [21] did not have available any large series of statistics from which to judge but made the statement that the fact that a patient with juvenile dementia paralytica had a father or mother with dementia paralytica might be incidental. If, however, he stated, the incidence of this form of syphilis among the parents or the marital partners of neurosyphilitic patients is greater than that for any unselected class of syphilitic persons, one may legitimately claim to have clinical evidence in favor of the existence of a neurotropic strain. Such figures have been presented in the present report, summarizing a large series of cases of juvenile dementia paralytica in which the number of instances in which the parents had dementia paralytica is far in excess of that in an unselected group of patients with neurosyphilis. On the other hand,

18. Strohmayer, W.: Familiäre Tabes auf erblich-degenerativer Grundlage, Neurol. Centralbl. **26**:754-756, 1907.

19. Burrow, J. L.: Familial Tabes Dorsalis, J. Neurol. & Psychopath. **1**:246, 1920.

20. Moore, J. E., and Keidel, A.: Studies in Familial Neurosyphilis: II. Familial Neurosyphilis from Various Extra-Familial Sources; a Clinical Contribution to the Question of Neurotropism, J. A. M. A. **80**:818-820 (March 24) 1923.

21. Stewart, R. M.: Juvenile Types of General Paralysis, J. Ment. Sc. **79**: 602-613 (Oct.) 1933.

Stewart pointed out the pertinent evidence that many siblings of patients with juvenile dementia paralytica acquire syphilis in other forms than neurosyphilis, a fact which we also have frequently observed.

SUMMARY

As stated at the beginning of this paper, our purpose has been to present further clinical evidence suggesting the existence of a neurotropic strain of S. pallida. We believe that before the problem can be definitely solved, it must be done experimentally. We regard the theory of familial predisposition as a thinly cloaked disguise for an unclear concept and believe that the mass of clinical evidence suggests definitely that the micro-organism itself must in some instances have a specific affinity for, or at least a tendency to reside in and carry on its destructive work on, the nervous tissue.

STUDIES IN DISEASES OF MUSCLE

III. METABOLISM OF CREATINE AND CREATININE IN MYASTHENIA GRAVIS, INCLUDING A STUDY OF THE EXCRETION OF NUCLEOSIDES AND NUCLEOTIDES

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In contrast to progressive muscular dystrophy, in which appreciable amounts of creatine usually are excreted (Milhorat and Wolff [1]), myasthenia gravis is associated often with little change in the metabolism of creatine and creatinine. Some observers have reported creatinuria and a diminished output of creatinine in myasthenia gravis, whereas other workers have observed patients in whom no excretion of creatine could be demonstrated and in whom the amounts of urinary creatinine appeared to be normal.

The present study, which is part of an investigation on the metabolism of creatine and creatinine in the various types of muscular disease, was undertaken to determine the factors which influence the output of creatine and creatinine in myasthenia gravis.

MATERIAL AND METHODS

The subjects were eleven patients, five of whom were seen at regular intervals for a period of from over three to four years. During the periods of observation the patients were in a special metabolism ward, where weighed diets free from creatine and creatinine could be given and the twenty-four hour specimens of urine could be carefully collected. The dietary control of the patients and the methods used in making the observations and chemical determinations have been described in the earlier reports of this series.[2]

From the Russell Sage Institute of Pathology, in affiliation with the Department of Medicine, the New York Hospital and the Cornell University Medical College.

1. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: I. Metabolism of Creatine and Creatinine in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **38**:992 (Nov.) 1937.

2. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: II. Effect of Varying Amounts of Ingested Creatine upon the Creatine Tolerance in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **39**:37 (Jan.) 1938; footnote 1.

The studies included the determination of: (1) the spontaneous output of creatine; (2) the output of creatinine; (3) the ability to retain ingested creatine (creatine tolerance); (4) the influence of remission and exacerbation of symptoms on the metabolism of creatine and creatinine, and (5) the effect of amino-acetic acid, ephedrine, prostigmin (the dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulfate), iodine and anterior pituitary extract on the output of creatine and the creatine tolerance.

SPONTANEOUS OUTPUT OF CREATINE

Seven of the patients eliminated creatine in relatively small amounts. The daily output of these patients varied from 0.01 to 0.076 Gm., amounts which are no larger than one often observes in normal women without muscular disease. Men, as discussed in the earlier reports, usually excrete no creatine, or only minimal amounts, whereas for women the excretion of small amounts of creatine (up to 0.08 Gm. per day) is not an uncommon finding. Five of the seven patients were females, and, moreover, they eliminated the largest amounts of creatine. The men, on the other hand, excreted only about 0.01 Gm. daily. Therefore, when the output of creatine often observed in normal subjects is considered, the variations seen in these patients with myasthenia gravis become even less pronounced.

The muscular disability of these patients varied from slight weakness and easy fatigability (e. g., S. H., with an output of 0.076 Gm. of creatine) to considerable generalized muscular weakness, with diplopia and difficulty in phonation and deglutition (e. g., M. J., with an output of 0.044 Gm. of creatine, and L. H., with an output of 0.016 Gm.). It is evident from this that moderate, or even severe, involvement of the muscles can occur in myasthenia gravis without any significant change in the spontaneous output of creatine. Furthermore, most of the patients studied during an acute exacerbation of the symptoms excreted no greater amounts of creatine than those observed during a remission (table). On the other hand, patient B. A., who showed serious and extensive muscular weakness and in whom the withdrawal of ephedrine was followed by an alarming increase in symptoms, had a higher amount of creatine in the urine than any other patient in this group. Patient J. S., who suffered from an acute and rapidly fatal form of myasthenia gravis, excreted the largest amounts of creatine of any patient in this series. Because of the serious state of his illness, none of the therapeutic measures could be discontinued; so the amount of creatine in the urine could be ascertained only while he was receiving amino-acetic acid. As will be discussed later in this report, administration of amino-acetic acid undoubtedly increased the output of creatine in this case. The spontaneous output of creatine must have been somewhat lower than the high value of 0.433 Gm. daily which was observed

TABLE 1.—*Effect of Ingested Creatine and Amino-Acetic Acid on the Excretion of Urinary Creatinine and Creatine in Myasthenia Gravis*

Patients*	Days in Period	Total Urinary Nitrogen Daily, Gm.	Urinary Preformed Creatinine Daily, Gm.	Urinary Creatine as Creatinine Daily, Gm.	Amino-Acetic Acid per Day, Gm.	Creatine		Preformed Creatinine per Kg. of Body Weight, Mg.
						Given, Gm.	Retained, Percentage	
Case 1, S. H., female, age 31, 50 Kg.	5	6.44	0.737	0.076				
	1	6.22	0.715	0.341	..	1.32	73	14.8
	3	6.46	0.750	0.008				
	4	9.26	0.695	0.144	20			
	2	10.09	0.769	0.594	20	1.32	10	
	2	8.50	0.762	0.214	20			
Case 2, J. S., male, age 14, 37.8 Kg.	1	16.08	0.823	0.433	30			
	2	15.65	0.730	0.974	30	1.32	0	
	3	15.35	0.668	0.308	30	....	..	20.6
	2	13.14	0.883	0.715	30	1.32	9	
Case 3, D. F., male, age 35, 68 Kg.	4	7.46	1.186	0.142	15			
	2	7.19	1.150	0.102	15	1.32	100	
	2	9.12	1.108	0.014	15	....	..	16.1
	2	9.44	1.109	0.344	..	1.32	52	
	2	9.96	1.174	0.133				
Case 4, B. A., female, age 48, 54 Kg.	4	7.49	0.919	0.164				
	2	5.72	0.920	0.330	..	1.32	65	17.0
	1†	9.65	0.857	0.298	20			
	2	10.23	0.956	0.687	20	1.32	22	
Case 5, M. J., female, age 31, 48 Kg.	4	....	0.921	0.046				
	1	....	0.884	0.378	..	1.32	67	19.2
Case 6, L. H., female, age 35, 49 Kg.	10	4.70	0.894	0.047				
	1	4.90	0.894	0.345	..	1.32	70	
	2	5.73	0.916	0.100	20	....	..	18.2
	1	6.20	0.880	0.410	20	1.32	38	
Case 7, M. T., female, age 40, 47 Kg.	1	7.62	0.768	0.132	20			
	1	6.16	0.665	0.433	20	1.32	70	16.3
	1	7.18	0.800	0.113	20			
	2	4.65	0.897	0.297				
Case 8, J. R., female, age 17, 48 Kg.	2	6.67	1.053	0.046				
	1	6.56	1.010	0.490	..	1.32	60	
	1	6.16	1.060	0.020				
	2	8.96	1.020	0.083	20	....	..	21.9
	2	10.30	1.020	0.915	20			
	1	7.12	1.050	0.250	20	1.32	17	
Case 9, M. N., female, age 36, 68.6 Kg.	5	8.00	1.214	0.054				
	2	9.05	1.246	0.322	..	1.32	46	
	2	9.82	1.242	0.032	..	....	..	17.7
	3	10.84	1.245	0.026	20			
	1	10.70	1.271	0.577	20	1.32	46	
	1	11.23	1.357	0.034	20			
Case 10, R. R., female, age 33, 96 Kg.	2	4.62	1.064	0.038				
	1	5.03	1.184	0.211	..	1.32	81	
	2	5.19	1.059	0.021	20			
	5	8.17	1.132	0.021	20	....	..	11.1
	1	9.00	1.245	0.281	20	1.32	74	
	2	7.64	1.020	0.020				
Case 11, H. S., male, age 34, 62 Kg.	3	7.79	1.640	0.010				
	1	6.70	1.710	0.045	..	1.32	96	
	2	7.80	1.665	0.010				
	1	11.25	1.665	0.015	30	....	..	26.4
	1	11.00	1.500	0.133	30	1.32	88	

* Cases 1 to 8 were observed during an exacerbation of symptoms. Patients J. S. (case 2) and M. T. (case 7) had a severe and rapidly fatal form of the disease. Cases 9 to 11 were studied during a remission of symptoms.

† Thirteenth day of administration of amino-acetic acid.

while the patient was receiving 30 Gm. of amino-acetic acid a day. However, comparison with the data for other patients who were receiving amino-acetic acid indicates a much higher excretion of creatine by this patient with a rapidly fatal form of the illness than one usually observes in cases of myasthenia gravis. Likewise, patient M. T., who also was observed during an acute and rapidly fatal form of the disease, had a high creatine output (0.297 Gm. per day).

CREATINE TOLERANCE

When moderate amounts of creatine (from 0.5 to 3 Gm.) are ingested by the normal man, all the creatine is retained, or only minimal amounts are excreted. In women exogenous creatine often elicits transitory creatinuria of slight degree. Of the ingested dose of creatine 10, or even 25, per cent may be excreted by normal women. Children may normally have an even lower creatine tolerance.

In each of the patients in this series, the ability to retain ingested creatine (creatine tolerance) was determined. Six of the ten patients retained over 70 per cent of the exogenous creatine and thus showed a creatine tolerance that must be regarded as normal, or only slightly impaired. One patient (M. N.), who was having a remission of symptoms, had a creatine tolerance of only 46 per cent, whereas patients M. J. and B. A., who had considerable muscular disability, showed a creatine tolerance of 76 and 65 per cent, respectively. Examination of the data given in the table discloses no significant difference in the creatine tolerance between patients with a remission and those with an exacerbation of muscular involvement. An exception to this general observation is found in two instances: (1) in patients with a rapidly fatal form of the disease and (2) in patients who are receiving amino-acetic acid. We discussed this effect of amino-acetic acid in a previous report.[1]

OUTPUT OF PREFORMED CREATININE

The amount of preformed creatinine excreted daily in the urine is generally regarded as an index of the total mass and efficiency of the muscles. In normal subjects, the largest amounts are eliminated by well developed men, whereas women and subjects with small muscles have a much smaller output. Furthermore, the output of creatinine is remarkably constant from day to day and in the main is independent of the food intake. A familiar way of expressing the creatinine output is the "creatinine index," or the number of milligrams of creatinine per kilogram of body weight eliminated in twenty-four hours. Sometimes the amount of creatinine nitrogen is used, but in these reports, the amount of creatinine itself has been employed. Many factors should be considered in interpreting the "creatinine index." Some of these, such as

obesity and the weight of the skeletal structures in relation to that of the muscle mass, have been considered in our first report.[1] When the necessary precautions are taken, the creatinine index constitutes a convenient way of comparing the creatinine outputs of a group of subjects.

In the table the creatinine indexes of the eleven patients in this series are given. Seven of the patients, it will be seen, had an index lower than is usually observed in normal subjects of the same sex and weight. On the whole, the creatinine output was lower in the patients who had the most impairment of muscular function. However, there was no definite correlation between the amount of muscular weakness and the diminution in creatinine output.

The low creatinine index of the patient R. R., who excreted large amounts of creatinine, is explained by her obesity. Patient J. S. had a creatinine output which was lower than normal but higher than that of most of the other patients in the series, although his condition was severe and rapidly fatal.

EFFECT OF AMINO-ACETIC ACID

Administration of amino-acetic acid to some patients with creatinuria increases the output of creatine. This is notably the case in persons with progressive muscular dystrophy, in which condition administration of amino-acetic acid can also decrease the creatine tolerance.

Ten of the patients with myasthenia gravis were given amino-acetic acid in amounts of from 15 to 30 Gm. daily, and the effect on the creatine output and the creatine tolerance was studied. In three patients having a remission of symptoms amino-acetic acid was without effect on either the output of creatine or the creatine tolerance. Of the seven patients to whom amino-acetic acid was given during a period of increased muscular fatigability four showed an increase in the excretion of creatine, and one did not. In one case, the administration of amino-acetic acid was not discontinued because the patient was seriously ill; in another patient (M. T.) the symptoms became much worse at the time the amino-acetic acid was omitted. An explanation for the higher excretion of creatine during this period of control is not evident. All six of these patients, however, retained less exogenous creatine when they were taking amino-acetic acid than during the period of control. This effect of amino-acetic acid on the retention of ingested creatine was not shown only by patients with an already appreciable impairment of the creatine tolerance. In fact, one patient (D. F.), who was able to retain all of an ingested dose of creatine when no amino-acetic acid was taken, retained only 52 per cent of the creatine when amino-acetic acid and creatine were administered together. A patient with a creatine tolerance of only 46 per cent during a period of comparative relief from symptoms

retained the same amount of ingested creatine when amino-acetic acid was given in addition. The output of preformed creatinine was unaffected by the administration of amino-acetic acid.

EFFECT OF EPHEDRINE ON METABOLISM OF CREATINE

The effect of ephedrine on the functional capacity of the muscles in myasthenia gravis was first reported by Edgeworth.[3] She noticed in a series of carefully controlled observations that the use of the drug was followed by improvement in the function of the muscles. Although several observers, notably Boothby,[4] have confirmed this finding, no data on the mechanism of the action of the drug have been presented. In the present investigation the effect of ephedrine was studied on the excretion of creatine and the creatine tolerance in two patients with myasthenia gravis and in one with progressive muscular dystrophy. The results were similar. No effect on the metabolism of creatine could be demonstrated by the methods employed.

In two patients with myasthenia gravis ephedrine sulfate influenced the muscular function, but no corresponding change in the creatine metabolism was noted. The level of the spontaneous output of creatine and the creatine tolerance were unchanged, and the effect of amino-acetic acid on the creatine tolerance was not modified. The administration of ephedrine to a patient with progressive muscular dystrophy influenced neither the muscular function nor the creatine tolerance. Also, the effect of amino-acetic acid on the creatine output and the creatine tolerance was unchanged.

EFFECT OF PROSTIGMIN ON METABOLISM OF CREATINE

Walker[5] recently observed definite improvement in the muscular function of patients with myasthenia gravis following the administration of physostigmine. Pritchard,[6] using prostigmin, a homolog of physostigmine, confirmed these findings. The improvement in each case was definite, but transitory, the effects of the drug disappearing during the course of eight hours. In this study the creatine output and creatine

3. Edgeworth, Harriet: A Report of Progress on the Use of Ephedrine in a Case of Myasthenia Gravis, J. A. M. A. **94**:1136 (April 12) 1930; The Effect of Ephedrine in the Treatment of Myasthenia Gravis: Second Report, ibid. **100**: 1401 (May 6) 1933.

4. Boothby, W. M.: Myasthenia Gravis: Effect of Treatment with Glycine and Ephedrine; Third Report, Arch. Int. Med. **53**:39 (Jan.) 1934; Myasthenia Gravis: Eighth Report, Tr. A. Am. Physicians **51**:188, 1936.

5. Walker, M. B.: Treatment of Myasthenia Gravis with Physostigmine, Lancet **1**:1200 (June 2) 1934.

6. Pritchard, E. A. B.: The Use of "Prostigmin" in the Treatment of Myasthenia Gravis, Lancet **1**:432 (Feb. 23) 1935.

tolerance were determined during seven periods of administration of prostigmin to three patients with myasthenia gravis and during two periods in which the drug was given to a patient with progressive muscular dystrophy. Each patient with myasthenia gravis was given subcutaneous injections of from 1.5 to 2 mg. of prostigmin daily, for periods of from four to five days. This amount had been shown to produce the greatest effect on muscular function. During these periods the creatine output and creatine tolerance were the same as during the periods used as controls. In one experiment the daily amount of urine was divided, so as to permit determination of the excretion of creatine during several periods of the day. These periods coincided with the period of maximal improvement in muscular function, the period during which the effects of the drug were wearing off and the period of depression which often followed the use of the drug. No effect of prostigmin on the output of creatine was found.

EFFECT OF IODINE ON OUTPUT OF CREATINE

Administration of iodine in the form of compound solution of iodine U. S. P. (1 cc. daily for ten days) was without effect on the creatine output of patient S. H. In this respect, patients with myasthenia gravis differ from those with exophthalmic goiter, in which the amount of creatine in the urine is diminished, or even abolished, by iodine.

EFFECT OF ANTERIOR PITUITARY EXTRACT ON METABOLISM OF CREATINE

Simon [7] has reported recently on the therapeutic use of anterior pituitary extract in two patients with myasthenia gravis. Both patients showed immediate and definite clinical improvement when the extract was administered. When the injections were discontinued, one of the patients soon reverted to his former condition, whereas the status of the second remained unchanged. It would appear that anterior pituitary extract had a beneficial effect in the first patient, as the administration of the substance was always followed by clinical improvement. However, in the case of the second patient it is probable that a spontaneous remission had occurred. In the present study, anterior pituitary extract was given to two patients. Patient M. J. (case 5) was given 1 cc. of the extract subcutaneously every day for fifteen days. Daily observations of the patient disclosed no change in the functional capacity of the muscles. No significant change in the output of creatine or the creatine tolerance was observed. The second patient, M. N., was given 1 cc. of anterior pituitary extract daily for fourteen days. No effect on

7. Simon, H. E.: Myasthenia Gravis: Effect of Treatment with Anterior Pituitary Extract; Preliminary Report, J. A. M. A. **104**:2065 (June 8) 1935.

the clinical picture could be demonstrated. The excretion of creatine, which was observed daily, and the creatine tolerance before and during administration of the extract were unchanged.

ABSENCE OF NUCLEOSIDES AND NUCLEOTIDES IN THE URINE OF A PATIENT WITH MYASTHENIA GRAVIS

Myasthenia gravis is associated frequently with hyperplasia of the lymphoid structures, which contain large amounts of the nucleic acids. The nucleic acid derivative adenylic acid plays an important rôle in the physiologic activity of skeletal muscle; it seemed of interest, therefore, to determine whether nucleotides or nucleosides are eliminated in myasthenia gravis. Accordingly, the following experiment was designed.

Twenty-eight liters of urine was used representing the output for fourteen days of patient M. N., with moderately severe myasthenia gravis. The patient had received 20 Gm. of amino-acetic acid daily, in addition to a diet free from meat. Tests on the urine were made by a procedure which is largely that of Embden and Zimmermann [8] as modified by Calvery.[9] For the isolation of adenine, which was also attempted, the method of Krüger and Salomon [10] was employed.

The urine was made alkaline by adding a suspension of calcium oxide in water. After removal of the precipitated phosphates, the supernatant fluid was treated with 1,400 cc. of a 20 per cent solution of copper sulfate, the solution being kept alkaline to litmus. The precipitate, which was removed by centrifuging the solution, was washed with a solution of calcium hydrochloride, suspended in warm water and decomposed with hydrogen sulfide. Precipitation with copper and treatment of the copper precipitate were then repeated. On addition to the filtrate of aqueous solution containing 36 Gm. of lead acetate, an immediate precipitate formed. As this procedure precipitates nucleotides, the precipitate was tested for pentose and for purine bodies. The results of the tests were all negative.

The solution was then made alkaline with ammonium hydroxide, and a copious white precipitate formed immediately. After standing five hours, the solution was centrifuged. The supernatant fluid (F 15-6) was used later in the procedure to be described. The precipitate was suspended in hot water and decomposed with hydrogen sulfide. After the removal of all the lead, the solution was filtered. The filtrate was aerated until free from hydrogen sulfide, treated with 60 cc. of a 25 per cent solution of lead acetate, and again made alkaline with ammonium hydroxide. The copious precipitate was removed by centrifuging, suspended in hot water and decomposed with hydrogen sulfide. The filtrate of this procedure was aerated until free from hydrogen sulfide and then concentrated on the steam bath to 15 cc. It was then decolorized with a prepared charcoal and further

8. Embden, G., and Zimmermann, M.: Ueber die Chemie des Lactacidogens, Ztschr. f. physiol. Chem. **167**:114, 1927; Ueber die Bedeutung der Adenylsäure für die Muskelfunktion: I. Das Vorkommen von Adenylsäure in der Skelettmuskulatur, ibid. **167**:137, 1927.

9. Calvery, H. O.: The Isolation of Adenosine from Human Urine, J. Biol. Chem. **86**:263, 1930.

10. Krüger, M., and Salomon, G.: Die Alloxurbasen des Harnes, Ztschr. f. physiol. Chem. **24**:364, 1898.

concentrated on the steam bath to a thin syrup. The syrup was precipitated thoroughly with a saturated alcoholic solution of trinitrophenol and, after standing overnight, was filtered over suction. The precipitate was recrystallized a few times from water, and the usual tests for its identification were performed. A sample of the precipitate was dissolved in a hot dilute solution of hydrochloric acid and the trinitrophenol removed by extraction with toluene. The aqueous solution was concentrated on the steam bath; tests for purine bodies gave negative reactions. Micro-analyses of the precipitate gave values corresponding to the composition of the ammonium salt of trinitrophenol.[11] The solution F 15-6, already referred to, was treated with hydrogen sulfide until all traces of lead were removed and was then filtered. The excess hydrogen sulfide was removed from the filtrate by aeration, and the solution was then made alkaline with ammonia and precipitated with ammoniacal silver. After standing overnight, this solution was centrifuged. The precipitate was suspended in hot water and decomposed with hydrogen sulfide. After filtration, the solution was aerated until free from all excess hydrogen sulfide and was concentrated on the steam bath to a few cubic centimeters, when a small amount of precipitate formed.

Both the solution and the precipitates gave negative reactions to color tests for purine bodies. Therefore, despite that hyperplasia of tissues which contain large amounts of nucleic acids is a common finding in myasthenia gravis, there was no increased excretion of either nucleosides or nucleotides in this patient.

COMMENT

Some observers (Bookman and Epstein;[12] Williams and Dyke;[13] Monrad-Krohn and Forsberg;[14] Berglund, Medes and Lohmann;[15] Adams, Power and Boothby;[16] Remen;[17] Harris and Brand;[18]

11. Prof. Karl Thomas, of the Physiologisch-Chemisches Institut, Leipzig, made these analyses.

12. Bookman, A., and Epstein, A. A.: The Metabolism in a Case of Myasthenia Gravis, with Considerations on the Administration of Calcium and of Glandular Preparations, Am. J. M. Sc. **151**:267, 1916.

13. Williams, B. W., and Dyke, S. C.: Creatinuria and Glycosuria in Myasthenia Gravis, Quart. J. Med. **15**:269, 1922.

14. Monrad-Krohn, G. H., and Forsberg, R.: Contributions to the Pathology of Myasthenia, Acta psychiat. et neurol. **5**:247, 1930.

15. Berglund, H.; Medes, G., and Lohmann, A.: The Effect of Hypercalcemia on the Creatin Output in Myasthenia Gravis, Proc. Soc. Exper. Biol. & Med. **25**:204, 1927.

16. Adams, M.; Power, M. H., and Boothby, W. M.: Chemical Studies in Myasthenia Gravis, Ann. Int. Med. **9**:823, 1936; Metabolism Studies in Myasthenia Gravis Before and After the Administration of Glycine, ibid. **9**:1330, 1936.

17. Remen, L.: Zur Pathogenese und Therapie der Myasthenia gravis pseudoparalytica, Deutsche Ztschr. f. Nervenh. **128**:66, 1932.

18. Harris, M. M., and Brand, E.: Metabolic and Therapeutic Studies in the Myopathies with Special Reference to Glycine Administration, J. A. M. A. **101**: 1047 (Sept. 30) 1933.

Schmidt,[19] and Gros [20]) have reported creatinuria in myasthenia gravis. On the other hand, patients in whom no excretion of creatine could be demonstrated have been observed by Diller and Rosenbloom; [21] McCrudden and Sargent; [22] Hellich and Tessenow; [23] Gibson, Martin and Buell,[24] and Harris and Brand.[18]

In most of the cases of myasthenia gravis in this study, only moderate amounts of creatine were eliminated, and the creatine tolerance was only moderately impaired. However, the two patients in whom the course of the disease progressed rapidly to a fatal termination excreted large amounts of creatine. Williams and Dyke [13] similarly found a high creatine output (0.449 Gm.) in a patient with fatal illness in whom the onset was acute and the course of the disease rapid. One such patient in this study showed a serious defect in the ability to retain ingested creatine. Adams, Power and Boothby [16] have emphasized the lack of uniformity in the chemical changes in myasthenia gravis. The data obtained for the patients in this report are in agreement with their findings.

Most patients seen during an exacerbation of symptoms excreted no greater amounts of creatine than did most of the other patients during a remission. Furthermore, the creatine tolerance in the two groups did not differ appreciably. However, in patients with exacerbation of symptoms a more serious defect in the metabolism could be demonstrated usually by the reaction to ingested amino-acetic acid. Further impairment of the creatine tolerance in this group usually followed ingestion of this substance.

Considerable muscular weakness and fatigability may occur in myasthenia gravis without any appreciable defect in the metabolism of creatine. On the other hand, during the acute and rapidly fatal form of the disease large amounts of creatine may be eliminated. Since wasting of the muscles is not a common finding in myasthenia gravis, the creatinuria cannot be related to this. In one case (that of J. S.) in which a serious

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19. Schmidt, E. O. G.: The Use of Glycine in the Treatment of Myasthenia Gravis, Ann. Int. Med. **7**:948, 1934.

20. Gros, W.: Zur Behandlung der Myasthenia gravis mit Glykokoll, München. med. Wchnschr. **81**:526 (April 6) 1934.

21. Diller, T., and Rosenbloom, J.: Metabolism Studies in a Case of Myasthenia Gravis, Am. J. M. Sc. **148**:65, 1914.

22. McCrudden, F. H., and Sargent, C. S.: Chemical Changes in the Blood and Urine in Progressive Muscular Dystrophy, Progressive Muscular Atrophy, and Myasthenia Gravis, Arch. Int. Med. **21**:252 (Feb.) 1918.

23. Hellich, I., and Tessenow, C.: Stoffwechseluntersuchungen bei "Myasthenia pseudo-paralytica," Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:219, 1933.

24. Gibson, R. B.; Martin, F. T., and Van Rennselaer Buell, M.: A Metabolic Study of Progressive Pseudohypertrophic Muscular Dystrophy and Other Muscular Atrophies, Arch. Int. Med. **29**:82 (Jan.) 1922.

defect in the metabolism was demonstrated, postmortem examination failed to reveal any evidence of muscular atrophy. It appears probable that the changes in the output and retention of creatine are related to changes in the functional capacity of the muscle. Patients with other types of muscular disease, such as progressive muscular dystrophy, who show similar amounts of creatine in the urine have evident wasting of the muscles.

Myasthenia gravis and exophthalmic goiter occasionally resemble each other clinically (Warner,[25] Oppenheim [26] and Cohen and King [27]). Creatinuria in exophthalmic goiter is common (Shaffer;[28] Palmer, Carson and Sloan,[29] and Shorr, Richardson and Wolff [30]). However, the level of the creatinuria is usually higher in this disease than in myasthenia gravis, and its reduction or abolition following the use of iodine (Palmer, Carson and Sloan [29] and Shorr, Richardson and Wolff [30]) does not occur in myasthenia gravis.

The output of preformed creatinine was moderately decreased in most patients in this series, but there was no correlation between the amount of muscular weakness and the reduction in elimination of creatinine. The reason for this diminution in the output of creatinine is not clear, since it appears not to be related to impairment in muscular efficiency and wasting of the muscles does not usually occur in myasthenia gravis. Boothby and his associates [16] stated that they were unable to observe any striking abnormalities in the excretion of creatinine, contrary to the interpretation in reports of earlier workers. The results of the present investigation confirm this opinion, and study of the data submitted by previous investigators shows the same moderate or slight reduction in the creatinine output in many patients. These results are in contrast to those found in progressive muscular dystrophy, in which there is often considerable reduction in the excretion of creatinine. The diminution in the output of creatinine in these patients is proportional to the reduction in the mass and efficiency of the muscles (Milhorat and Wolff [1]).

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25. Warner, F.: Ophthalmoplegia Externa, Complicating a Case of Graves' Disease, M. Times & Gaz. **2**:541, 1882.

26. Oppenheim, H.: Die myasthenische Paralyse (Bulbärparalyse ohne anatomischen Befund), Berlin, S. Karger, 1901.

27. Cohen, S. J., and King, F. H.: Relation Between Myasthenia Gravis and Exophthalmic Goiter, Arch. Neurol. & Psychiat. **28**:1338 (Dec.) 1932.

28. Shaffer, P. A.: Protein Metabolism in Exophthalmic Goiter, J. Biol. Chem. **3**:xiii, 1907-1908.

29. Palmer, W. W.; Carson, D. A., and Sloan, L. W.: The Influence of Iodine on Excretion of Creatine in Exophthalmic Goiter, J. Clin. Investigation **6**: 597, 1929.

30. Shorr, E.; Richardson, H. B., and Wolff, H. G.: The Nature of the Muscular Weakness in Graves' Disease, J. Clin. Investigation **12**:966, 1933.

Further evidence of the comparative lack of relationship that exists between the impairment in muscular function and the creatine output and creatine tolerance in myasthenia gravis is obtained from the studies with ephedrine and prostigmin. Although both these substances increased the muscular efficiency in the patients who were studied, no accompanying changes in the metabolism of creatine could be demonstrated. One of us (A. T. M.)[31] and Boothby and his associates [16] have likewise reported that the administration of ephedrine was without effect on the output of creatine. Considerable changes in the muscular function of patients occurred after the use of prostigmin, but no effect on the creatine output was noted either in the period of twenty-four hours or in short periods which coincided with maximal changes in muscular function. Much reliable information on the action of physostigmine and its homologs has been presented by the researches of Dale and his colleagues, but little is known regarding the action of ephedrine in the physiologic behavior of muscle. Whatever the mechanism of this action may be, it does not affect the creatine output or the creatine tolerance.

The two patients reported on by Simon who received anterior pituitary extract showed improvement in symptoms within two days; the two patients in this study showed no clinical change in fourteen days and no change in the creatine output or the creatine tolerance. While no change in the metabolism of creatine was effected by the anterior pituitary extract employed, it is likely that the defect in the creatine metabolism may be accentuated if sufficiently large doses of an anterior pituitary extract containing large amounts of the thyrotropic hormone are given. The extract employed contains no thyrotropic hormone. Pugsley, Anderson and Collip [32] increased the creatine output of dogs by the injection of thyrotropic hormone. However, a commercial extract of anterior pituitary said to contain the growth hormone which had considerable amounts of the thyrotropic factor had no effect on the creatine output of a patient with progressive muscular dystrophy, when 1 cc. was given daily for ten days or on that of a patient with myasthenia gravis, when 2 cc. of the extract was given daily for twenty days. In both the patients the symptoms likewise were unchanged. If anterior pituitary extract has any therapeutic value in myasthenia gravis (and this has not been demonstrated adequately), it seems unlikely that

31. Milhorat, A. T.: Effect of Glycocoll and Ephedrine in Myasthenia Gravis, Am. J. Physiol. **109**:75, 1934.

32. Pugsley, L. I.; Anderson, E. M., and Collip, J. B.: The Effect of Thyreotropic Hormone and of Dessicated Thyroid upon Creatine and Creatinine Excretion, Biochem. J. **28**:1135, 1934.

its value is due to the thyrotropic hormone. Patients M. N. and M. O. appear to have been affected adversely when thyroid substances were administered.

It is interesting that no nucleotides or nucleosides were found in the urine of patient M. N., who showed definite impairment in muscular function. Calvery [9] recently recovered a small amount of the nucleoside adenosin from 80 liters of mixed urine of supposedly normal subjects, but he was unable to conclude whether small amounts of the substance are excreted normally or whether the adenosin was eliminated by only a few of the subjects. The findings reported here do not exclude the possibility that exceedingly small amounts of any of these substances are excreted in myasthenia gravis and that they could be isolated if very large quantities of urine were used. Thus, Krüger and Salomon [10] recovered small quantities of several purine substances from the mixed urine of unclassified patients when 10,000 liters of urine was used. However, the conclusion appears to be justified that by patient M. N., with moderately severe myasthenia gravis, no appreciable quantities of nucleotides or nucleosides were eliminated. This is of interest, since the lymphoid structures and thymus, which are enlarged in a high percentage of cases of myasthenia gravis (Mandelbaum and Celler [33] and Norris [34]), contain large amounts of nucleic acids and the nucleic acid derivative adenylic acid is an important component in the chemical activity of striated muscle.

SUMMARY

In most cases of myasthenia gravis only slight or moderate amounts of creatine are eliminated, and the creatine tolerance is only moderately impaired. Patients during a remission and those during an exacerbation of muscular involvement do not differ appreciably in the amount of defect in creatine metabolism. However, patients in whom the course of the disease progresses rapidly to a fatal termination often excrete large amounts of creatine and show a more serious defect in the ability to retain ingested creatine.

The defect in the creatine tolerance usually can be exaggerated during an exacerbation of symptoms by the ingestion of amino-acetic acid but usually is not affected during periods of remission.

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33. Mandelbaum, F. S., and Celler, H. L.: A Contribution to the Pathology of Myasthenia Gravis: Report of a Case with Unusual Form of Thymic Tumor, J. Exper. Med. **10**:308, 1908.

34. Norris, E. H.: The Thymoma and Thymic Hyperplasia in Myasthenia Gravis with Observations on the General Pathology, Am. J. Cancer **27**:421, 1936.

In myasthenia gravis the excretion of creatinine is not usually affected significantly. The diminution in the creatinine output shown by many patients is small, or only moderate.

Ephedrine and prostigmin have no effect on either the creatine output or the creatine tolerance, even during their maximal effect on the clinical symptoms.

No nucleosides or nucleotides were found in the urine of a patient with moderately severe myasthenia gravis.

CONCLUSIONS

In patients with myasthenia gravis there is only slight abnormality in the creatinine metabolism, except possibly just before death. The metabolism of creatine, though normal during remissions, is usually abnormal during exacerbations.

These metabolic disturbances are usually of less severity than the clinical symptoms, but they may vary with the degree of impairment of the muscular function, i. e., patients with the greatest disturbance in creatine metabolism are often those with the greatest degree of impairment in muscular function.

Disturbances in creatine metabolism do not precede the onset of exacerbations but, as a matter of fact, make their appearance after there is an obvious decline in muscular function.

In the instances in which the creatine metabolism is abnormal during a clinical exacerbation, sudden improvement of muscular function through the use of physostigmine or ephedrine is not associated with return to the normal state of creatine metabolism. Moreover, in the instances in which there is disturbance in the metabolism of creatine despite radical improvement in muscular function after administration of physostigmine or ephedrine, the improvement is temporary if the metabolism of creatine remains abnormal.

In short, it would seem that the fundamental metabolic disturbances in myasthenia gravis are not centered in the metabolism of creatinine and creatine but that the metabolism of creatine is involved secondarily when the abnormal process has become severe. Furthermore, once these metabolic processes are seriously involved, the prognosis for life is grave.

REPORT OF CASES

CASE 1.—S. H., a milliner aged 31, was admitted to the New York Hospital on Nov. 14, 1932, complaining of difficulty in eating and speaking, drooping of the eyelids, inability to shut her eyes tightly, weakness of the muscles of the back and neck and easy fatigability of all muscles. She had had these difficulties for eight years, except for a period of remission during which muscular function was satisfactory. Eight years ago (1924) the patient first began to find difficulty in pronouncing the explosive consonants and noticed that her voice had a nasal

quality and that she was unable to pucker her lips. Liquids regurgitated through her nose. The illness began with a severe sore throat. There were four recurrences, including the present illness. During the intervals there was increase in function of the weak muscle groups. The family history was noncontributory and the past personal history otherwise irrelevant.

Examination revealed defects essentially as described by the patient, with especial weakness of the cervical and erector spinae muscles. No wasting was noted. The reflexes disappeared readily on striking the tendon repeatedly. The patient weighed 50 Kg.

Case 2.—J. S., a school boy aged 14, was admitted to the New York Hospital on July 26, 1933, complaining of difficulty in speaking of from two to three months' duration and inability to swallow for one week. The onset of the present illness was gradual and was marked by fatigue, noted chiefly in the arms when he was playing ball. This was followed by inability to speak distinctly, which was most pronounced in the evening. Articulation was clearest in the morning. Three or four weeks before his admission (July 1) the patient "caught cold" and began to raise mucoid, stringy sputum, which on two occasions was streaked with blood. A week before his admission (July 19) there was difficulty in swallowing, with inability to cough or raise his sputum, so that he frequently experienced an alarming sensation of choking. His past personal history was irrelevant except that he had had congenital torticollis, which was corrected at the age of 8 years. He had had a tonsillectomy the same year. The family history was noncontributory.

Examination revealed emaciation and pallor, fixed facial expression, slight drooping of both upper eyelids and inability to close the mouth completely or to talk, whistle, swallow or cough. The tongue could be fully protruded. There were generalized weakness and ready fatigability of varying intensity, most marked in the muscles of the face, pharynx, back and legs.

During his stay in the hospital the patient was given adequate amounts of fluids and nourishment by nasal catheter. Ephedrine and amino-acetic acid were administered. During the first week his strength increased, and he breathed comfortably. He was able to close his eyes more tightly, wrinkle his forehead, protrude his tongue and speak more clearly. Swallowing continued to be difficult, and feeding by tube was maintained. However, on the eighth day after admission he had a recurrence of the infection of the upper respiratory tract, with febrile reaction, and within forty-eight hours he died of pulmonary edema.

Postmortem examination revealed slight atrophy of the intercostal muscles and generalized lymphoid hyperplasia. Sections of the diaphragm and the intercostal and pectoralis major muscles showed that the muscle fibers were of normal size and the cross-striations visible. The nuclei were not remarkable except that in many areas there appeared to be proliferation of nuclei. In these areas, in addition to the peripheral nuclei, large, vesicular nuclei were seen in the central portion of the muscle fibers. There were several focal infiltrations of lymphocytes in the muscle tissue and scattered infiltration between the muscle bundles. Numerous cells, with irregular, pyknotic nuclei, were seen about the muscle fibers; these, however, did not resemble polymorphonuclear leukocytes. Sections stained with Best's carmine stain did not show the presence of glycogen granules in the tissue. The patient weighed 37.7 Kg.

Case 3.—D. F., a man aged 35, was first observed by us in August 1933. He had had good health until September 1930, when he first noted occasionally a nasal quality of his voice and some difficulty in swallowing. A short time later the

left eyelid began to droop, and there developed weakneess of the muscles of the face and neck. The weakness gradually progressed, and during the following year (1931) the legs, thighs and arms became involved. Climbing stairs became impossible, and later walking was difficult. He tired easily, after even slight exertion. The past history was irrelevant except that he had been an athlete (on the college crew). The family history was noncontributory.

Examination in October 1932 showed bilateral facial weakness. The palate moved poorly and was easily exhausted. The tongue could not be protruded, and after a few words speech became unintelligible. Respiration was accomplished mainly by the diaphragm, with the use of accessory muscles in forced inspiration. Practically all muscles of the extremities showed considerable weakness and fatigued rapidly after activity. The tendon reflexes were normal, except that they disappeared after the tendon was tapped a few times. No sensory defect could be demonstrated. In October 1932 the patient was given 15 Gm. of amino-acetic acid daily, after which the symptoms improved. In August 1933 the studies on creatine were made. The patient's weight was 68 Kg.

CASE 4.—B. A., a saleswoman aged 48, entered the New York Hospital on Nov. 10, 1933, complaining of generalized muscular weakness of three years' duration. In August 1931 she first noticed weakness of the arms. Since that time muscular weakness had become generalized, involving speech and swallowing and, to some extent, respiration. This weakness had progressed with occasional remissions and exacerbations, which were usually worse during menstruation. The patient had been taking ephedrine for several months. The family and past histories were noncontributory. When, on her admission to the hospital, ephedrine was discontinued, she promptly became very weak and had great difficulty in swallowing. Ephedrine was given in combination with amino-acetic acid, and in four days she improved markedly.

Examination on admission revealed ptosis of both lids, strabismus, tremor of the tongue, indistinct speech and bilateral facial weakness. The tendon reflexes were at first hyperactive but disappeared when the tendon was struck repeatedly. The muscles of the extremities were weak and fatigued easily. No fibrillation was noted, and sensation was normal. There was no atrophy of the muscles; the thyroid gland was palpable. The patient's weight was 54 Kg.

CASE 5.—M. J., a telephone operator aged 31, was admitted to the New York Hospital on Oct. 29, 1934, complaining of muscular weakness and diplopia. Three months before her admission she noticed that her right hand had suddenly become weak and that she was unable to turn the dial of the telephone. After resting for fifteen minutes, however, the muscular power returned. However, for the next two weeks she had several similar attacks of weakness. At about this time she began to have double vision whenever the eyes were used a good deal. About one month before her admission to the hospital there developed intermittent weakness of the muscles of the arms, which came on whenever she tried to comb her hair or dress. In addition, she was fatigued easily after moderate activity. During a menstrual period at about this time, she had difficulty in swallowing and speaking. Thereafter the symptoms continued unchanged, with ready fatigability of most of the muscles and occasional diplopia and difficulty in swallowing. The menstrual periods were associated with an increase in all the symptoms.

The family and the past personal history were irrelevant. Significant findings on physical examination were: some limitation of the movements of the eyes on looking upward, moderate ptosis of both lids, apparent only after the eyes had been closed and opened many times and ready fatigability of the muscles of the arms.

Case 6.—L. H., a housewife aged 34, was admitted to the New York Hospital on April 14, 1935, complaining of diplopia for seven years and weakness of the arms and legs for six and one-half years. Seven years before admission the patient began to have intermittent diplopia, which has persisted up to the present. Six months after the onset of double vision she noticed that her legs tired more easily, and a short time later the muscles of the arms were fatigued easily after exertion. These symptoms varied in degree from time to time; on some days she felt fairly strong, and on others her weakness was considerable.

Two years before admission to the hospital the patient noticed that her voice had a nasal character; liquids regurgitated through her nose when she tried to swallow, and her face became expressionless. With varying degrees, the symptoms persisted until the time of her admission. During a pregnancy of six weeks (terminated by medication) the symptoms were much improved. The past personal history was irrelevant. A daughter has diabetes mellitus. Physical examination showed weakness of the extra-ocular and orbital muscles and a nasal quality of the voice. The peroneal muscles were weak. The tendon reflexes were hyperactive and not readily fatigued. The patient's weight was 49 Kg.

Case 7.—M. T., a housewife aged 40, entered the New York Hospital on Dec. 18, 1936. One month before her admission she had a sudden onset of weakness of the muscles of the neck, with difficulty in swallowing. The weakness rapidly increased and extended to involve the muscles of respiration. The patient had several episodes of severe respiratory difficulty, during which she became cyanotic. On a few occasions she had transitory diplopia. She entered the United Hospital in Port Chester, N. Y., where she was placed in a respirator and given prostigmin. On Dec. 18, 1936, she was transferred to the New York Hospital. Examination showed extreme difficulty in respiration. The intercostal muscles were weak, and respiration was accomplished with the aid of many accessory muscles. During respiration the abdomen did not move, suggesting paralysis of the diaphragm. There was no diplopia or ptosis. The muscles of the face moved well, but those of the jaw showed weakness. There was considerable weakness of the muscles of the neck. The extremities were not involved except for slight weakness of the muscles of the upper portions of the arms. The family history was irrelevant. Fourteen years ago the patient had had an attack of weakness in both arms, which lasted for only a few days. Otherwise, the past personal history was noncontributory.

Subsequent Course.—The patient was given prostigmin to control the episodes of extreme respiratory difficulty. For about a month the course was satisfactory. The paroxysms of difficult respiration became less frequent, and the patient was able to take adequate nourishment. However, the symptoms thereafter increased in severity. The muscular weakness became more generalized and the respiratory difficulty more severe, and the patient was unable to swallow. Prostigmin, which had relieved many of her symptoms, was now without therapeutic effect, and she had to be placed in the respirator. The heart action became very weak, and on a few occasions the pulse was barely perceptible. On January 24, the thirty-seventh day after her admission, the patient died. Her weight was 47 Kg.

Case 8.—J. R., a girl aged 17, was admitted to the New York Hospital on Feb. 1, 1937, complaining of generalized muscular weakness of three years' duration. Three years before admission she had noted an insidious increase in fatigability. At first she tired more easily when she engaged in gymnastic exercises. Soon after, she noted weakness in climbing stairs, and difficulty in raising

the arms to comb her hair. About two and one-half years before admission she first noted diplopia and then difficulty in swallowing and ptosis. Shortly after this, her jaw tired easily when she was chewing.

In October 1934 she was seen at the Neurological Institute, where she was given amino-acetic acid and ephedrine, with some improvement in symptoms. In September 1935, she started to take prostigmin. Since then her condition has fluctuated. On some days she has been so weak as to make it necessary to remain in bed; at other times she has been able to walk about the house all day without much fatigue. Transitory diplopia has occurred every few days since the onset of the illness.

The past personal history is noncontributory. A twin sister is in good health and has never had similar symptoms. Physical examination revealed weakness and easy fatigability of the muscles of the face, neck and extremities. There was no abnormal limitation of the eyes on looking up. The eyelids drooped slightly. The face was flat and expressionless, and the movements of the jaw were weak. The patient could not lift her arms above her head nor maintain them in a raised position when they were placed passively in this position. She tired easily and had to limit all activity. Her weight was 48 Kg.

CASE 9.—M. N., a housewife aged 36, entered the New York Hospital on Dec. 4, 1932, complaining of difficulty in raising the right eyelid and weakness of the muscles of the shoulders, particularly the right, when she combed her hair. The present complaints had their onset in 1931 and had persisted with remissions since that time. In December 1930 and in April 1931 the patient had an episode of acute iritis, during which the right eye became red and painful. In January 1931 she first noted diplopia on looking to the extreme right. In March 1932 and in June 1932 she had an attack of transient blindness in the right eye, lasting from five to ten minutes. She had severe diplopia in July 1932. Ptosis of the right eye improved gradually and had disappeared by October 1932. The left eye became slightly involved in this condition, but never as fully as the right. The patient's difficulty with her eyes and arms became worse when she was generally tired or overworked. There had been occasional attacks of sharp, throbbing pain over the right eye. She also complained of weakness of all muscle groups, with fatigability as an outstanding feature. The patient was suggestible, and the degree of weakness was difficult to evaluate. Except for acute exanthems in childhood, the past history was irrelevant. The family history was noncontributory.

Examination revealed: difficulty in upward gaze, particularly of the right eye, with drooping of the right eyelid; ready fatigability and prostration, and weakness of the perioral, and, particularly, of the right shoulder girdle muscles. The tendon reflexes were obtained but disappeared when attempts were made to elicit them repeatedly. The patient's weight was 68.6 Kg.

Subsequent Course.—In March 1934 the patient collapsed suddenly and complained of choking sensations, uncertainty of gait and bilateral ptosis, which was greater on the right than on the left. Examination revealed loss of ability to elevate the eyes and fatigability of all muscle groups of the extremities. The abdominal reflexes were present. She had difficulty in swallowing. Subsequently, she recovered the function of the muscles.

CASE 10.—R. R., a housewife aged 33, entered the New York Hospital on July 5, 1934, with a history of intermittent weakness of the muscles for about ten years, beginning at the age of 23 (1924). The onset of each attack was usually insidious, but in four instances it was sudden. During these attacks the patient was fatigued easily and at times had diplopia and was unable to walk or swallow food. The

menstrual periods were irregular and were always associated with increase in muscular weakness. At the age of 25, two years after the onset, the patient became free from all symptoms for two and one-half years. The past history was otherwise irrelevant. The family history was noncontributory.

On examination it was noted that the patient spoke with slight slurring, and after talking or chewing for a few minutes further movements of the mouth were impossible. There was slight difficulty in sustaining a hand clasp or in walking upstairs. The tendon reflexes were readily elicited, however, even after repeated stimulation. No sensory defect could be demonstrated. The basal metabolic rate was —11 per cent; the weight was 96 Kg.

Case 11.—H. S., a broker aged 34, was admitted to the New York Hospital on April 5, 1935, complaining of weakness of the arms and legs for two years and difficulty in speaking for nine months. Two years before admission the patient had noted the first symptoms, after a disappointment in business and an infection of the upper respiratory tract. The muscles of the arms and legs were weak and tired easily. These symptoms continued unchanged until nine months before admission, when the patient began to have difficulty in speaking. The voice was weak, and he noticed that he tired readily. Shortly after, he began to have increasing difficulty in swallowing food; at times the food was regurgitated through the nose. For the seven months prior to his admission there was occasional diplopia. At the time of his admission most of the symptoms had improved; there was no diplopia, difficulty in swallowing or significant fatigability of the muscles.

Physical examination revealed slight ptosis of both lids. The extra-ocular movements were normal. The facial muscles were weak and moderately expressionless. There was slight weakness of the muscles of the extremities. The weight was 62 Kg.

News and Comment

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

At the meeting of the American Board of Psychiatry and Neurology, Inc., New York, Dec. 29 and 30, 1937, the following candidates were granted certificates:

PSYCHIATRY AND NEUROLOGY: Loren W. Avery, Chicago; A. A. Barron, Charlotte, N. C.; Aaron Bell, New York; Robert M. Bell, Taunton, Mass.; Albert Brawner, Smyrna, Ga.; Earl C. Chesher, New York; Stanley Cobb, Boston; Henry O. Colomb, Middletown, Conn.; Fred J. Conzelmann, Stockton, Calif.; Julia M. Donahue, Massillon, O.; Edwin J. Doty, New York; Samuel H. Epstein, Boston; Frederic Farnell, Providence, R. I.; Hiland L. Flowers, New York; Erel L. Guidone, Harding, Mass.; Earl K. Holt, Medfield, Mass.; Edgerton Howard, Boston; William N. Hughes, Providence, R. I.; Eugen Kahn, West Haven, Conn.; Gordon R. Kamman, St. Paul; William V. McDermott, Salem, Mass.; James F. McFadden, St. Louis; John C. McKinley, Minneapolis; Joseph C. Michael, Minneapolis; Joseph J. Michaels, Boston; Abraham M. Ornsteen, Philadelphia; Gerald Pearson, Philadelphia; Louis Pillersdorf, Cleveland; Harry C. Podall, Norristown, Pa.; Percy P. Poliak, New York; Charles Rosenheck, New York; Edward A. Sharp, Buffalo; Paul Sloane, Philadelphia; E. Rogers Smith, Indianapolis; Albert W. Stearns, Boston; Edward A. Strecker, Philadelphia; William J. Tiffany, Albany, N. Y.; Conrad Wall, Worcester, Mass.; David E. Warren, Passaic, N. J.; Walter C. Weigner, Providence, R. I.; Cornelius Wholey, Pittsburgh; Julian M. Wolfsohn, San Francisco; S. Bernard Wortis, New York; Morris Yorshis, Worcester, Mass.

PSYCHIATRY: Franz Alexander, Chicago; Velma H. Atkinson, Hathorne, Mass.; Irma Bache, Boston; Walter E. Barton, Worcester, Mass.; Olive T. Baskett, Retreat, Pa.; Joseph R. Blalock, New York; Emory J. Brady, Colorado Springs, Colo.; Rupert A. Chittick, Waverley, Mass.; Theodore L. Dehne, Philadelphia; Julia M. Donahue, Massillon, Ohio; Lewis Doshay, Bronx, N. Y.; John E. Edelstein, Brentwood, N. Y.; Malcolm Farrell, Waltham, Mass.; John N. Frederick, Pittsburgh; Salomon Gagnon, Waltham, Mass.; Arthur J. Gavigan, Worcester, Mass.; Jacob Goldwyn, Worcester, Mass.; Ransom Greene, Waverley, Mass.; Richard Hutchings, Utica, N. Y.; William C. Inman, Hathorne, Mass.; Paul H. Jordan, Worcester, Mass.; Milton Kirkpatrick, Worcester, Mass.; Clifford W. Mack, Livermore, Calif.; Russell G. MacRobert, New York; Edwin E. McNiel, New York; Horatio W. Newell, Baltimore; Roger G. Osterheld, Taunton, Mass.; Charles S. Raymond, Wrentham, Mass.; William A. Scott, Kalamazoo, Mich.; Philip Solomon, Boston; Conrad S. Sommer, Chicago; Johan van Ophuijsen, New York; Edgar C. Yerbury, Boston.

NEUROLOGY: James A. Brussel, Brentwood, N. Y.; David B. Davis, Grand Rapids, Mich.; Robert A. Groff, Philadelphia; Ezra V. Hahn, Indianapolis; William H. Haines, Chicago; Arthur H. Jackson, Waterbury, Conn.; Karl A. Menninger, Topeka, Kan.; Clarence W. Olsen, Los Angeles; Mabel D. Ordway, Boston; Winfred Overholser, Washington, D. C.; Raul Pietri, New York; John H. Scharf, New York; Samuel E. Soltz, New York; Calvert Stein, Palmer, Mass.; Charles S. Woodall, Waverley, Mass.

SPECIAL NOTICE: Dr. Lee W. Darrah, East Gardner, Mass., was certified in Psychiatry June 2, 1937. His name, unfortunately, was omitted from the list.

Abstracts from Current Literature

Anatomy and Embryology

THE NUMBER OF GANGLION CELLS IN THE DORSAL ROOT GANGLIA OF THE SECOND AND THIRD CERVICAL NERVES IN HUMAN FETUSES OF VARIOUS AGES. MARY E. MCKINNISS, Anat. Rec. **65**:255 (June) 1936.

Counts were made of the cells in the second and third cervical dorsal root ganglia in seven human fetuses with mean menstrual ages ranging from 7½ to 13 weeks. There were more cells and fewer mitoses in the older ganglia. The third cervical ganglion was always larger than the second, but there was no correlation as to the side.

RIOCH, Boston.

THE ANATOMY OF THE HYPOPHYSIS OF WHALES. GEORGE B. WISLOCKI and E. M. K. GEILING, Anat. Rec. **66**:17 (Aug.) 1936.

Wislocki and Geiling describe the gross and microscopic anatomic features, the meningeal relations and the weights of the hypophyses of four species of the Cetacea. The anterior and neural lobes are separated and encapsulated by a fold of the leptomeninges. There is no discernible pars intermedia. The pars tuberalis is small, and its cells stain faintly. The blood supply is rich, and a portal system of veins passes from the stalk to the pars anterior. The cytologic picture of the anterior and neural lobes conforms to that of other mammals.

RIOCH, Boston.

CYTOLOGICAL STUDIES BY THE ALTMANN-GERSH FREEZING-DRYING METHOD: IV. THE STRUCTURE OF THE MYELIN SHEATH OF NERVE FIBERS. N. L. HOERR, Anat. Rec. **66**:91 (Aug.) 1936.

By means of the freezing-drying technic and by clearing in vacuo in glycerin or paraffin oil, Hoerr shows that the myelin sheath of nerves is homogeneous. The neurokeratin network and other variable figures in the myelin can be produced by exposure of the frozen-dried tissue to appropriate fixatives.

RIOCH, Boston.

INTRA-UTERINE RESPIRATORY MOVEMENTS OF THE HUMAN FETUS. F. F. SNYDER and M. ROSENFELD, J. A. M. A. **108**:1946 (June 5) 1937.

Snyder and Rosenfeld point out that respiration is not initiated in the child at birth but extends far back into embryonic life. Instead of a state of complete apnea during intra-uterine life, the human fetus shows spontaneous respiratory movements for periods lasting many minutes. The capacity of the human fetus to show respiratory movements within the uterus for brief intervals was recognized by Schultze. Respiratory failure of the new-born, or asphyxia neonatorum, must be regarded as suppression of previous activity rather than failure of a new mechanism to begin functioning at birth. In the apneic new-born child the question is not what causes the first breath but what factors have been superimposed to suppress the continuation of respiratory movements. With regard to the causes of respiratory failure, it may be emphasized that the fetal respiratory system before birth has been demonstrated to have a peculiar sensitivity to the depressant effect of anoxemia and narcosis. Both of these factors belong to the period preceding delivery. To deal with them at that time by efforts to maintain adequate oxygenation and by caution in the choice and use of anesthetic agents would be more effective than later attempts at resuscitation. The aspiration of amniotic fluid is not an accidental complication of labor but must be viewed as a normal

consequence of fetal respiration. The normal development of the alveoli may be complicated by the presence of amniotic fluid containing débris of excessive amount or abnormal type. A mechanical obstruction of bronchioles brought about during embryonic life may interfere with the normal flow into the lung of amniotic fluid and result in incomplete dilatation of alveoli; i. e., atelectasis. Certain types of débris, such as cells, meconium and sebaceous matter, may be injurious not only as foreign bodies but as chemical irritants. In view of the rapid exchange of fluid between the pulmonary alveoli and the amniotic sac, bacterial contamination exposes the alveoli to immediate invasion by a current of infected fluid. The pathogenesis of intra-uterine pneumonia may be clearly reconstructed in many cases as a complication of normal intra-uterine respiration.

EDITOR'S ABSTRACT.

A PUPILLO-CONSTRICTOR AREA IN THE CEREBRAL CORTEX OF THE CAT AND ITS RELATIONSHIP TO THE PRETECTAL AREA. RALPH W. BARRIS, J. Comp. Neurol. **63**:353 (Feb.) 1936.

The purpose of this study was to determine in the cat the course and termination of corticifugal fibers from the cortical pupilloconstrictor area and to determine the source of any corticipetal fibers which might reach this cortical pupilloconstrictor area from the underlying brain stem. Bilateral and approximately equal constriction of the pupils was obtained on stimulation of a restricted area on the medial and lateral surfaces of the inferior portion of the posterior lateral gyrus in each of ten cats. After destruction of this area, the Marchi technic was used to trace degenerated fibers to three nuclear regions of the brain stem: (1) pretectal area, (2) the stratum opticum of the superior colliculus and (3) the pontile nuclei.

A small electrolytic lesion was placed in the pretectal area of each side of the brain. The degenerated fibers were studied with the Marchi technic. Degenerated fibers were seen leaving the pretectal area and following a laterally directed course along the stratum zonale, to reach the superior thalamic radiation and the underlying white substance of the inferior portion of the posterior lateral gyrus.

ADDISON, Philadelplhia.

AN EXPERIMENTAL STUDY OF THE RÔLE OF OPTIC CUP AND OVERLYING ECTODERM IN LENS FORMATION IN THE CHICK EMBRYO. LLOYD E. ALEXANDER, J. Exper. Zoöl. **75**:41 (Jan.) 1937.

Careful analysis of the origin of the lens of the vertebrate eye has been carried out only in the Amphibia. This problem was studied, therefore, in chick embryos. Grafts of the whole or parts of the optic anlages and the overlying ectoderm were made in the chorio-allantoic membrane or in the body wall. Grafts from all stages up to that of 40 somites, except the presomite and early somite stages, grew and differentiated. Both the prospective sensory and prospective tapetal layers of the retina were equipotential up to the 36 somite stage, when the sensory layer showed less capacity for differentiation than the tapetal. Lenticular cells seldom differentiated in chorio-allantoic grafts. Lenses and lentoid bodies were formed from anlages transplanted from donors up to the 40 somite stage; lenses were formed in the head, neck or trunk region of the host up to the 4 somite stage; after this, only in the head and neck region. Lenses regenerated from the transplant were induced from the host epidermis or were joint products of both factors. Both optic tissue and undifferentiated ectoderm seemed to be necessary in the formation of lenses. In chorio-allantoic grafts the necessary junction of overlying ectoderm and optic tissue is probably seldom realized.

WYMAN, Boston.

PRESENCE OF AFFERENT FIBERS IN THE HYPOGLOSSAL NERVE. A. A. TARKHAN, Arch. f. Psychiat. **105**:475 (Oct.) 1936.

The hypoglossal nerve in the dog and cat contains both sensory and motor fibers, the former being proprioceptive. The sensory fibers, in contradistinction to the motor, undergo partial crossing in the medulla oblongata. The central

route of the afferent fibers of the lingual nerve are definitely related to the nucleus of the hypoglossal nerve. The presence of sensory fibers in the twelfth nerve was demonstrated by an increase in the blood pressure and by reflex movements of the tongue following irritation of the central stump of a severed nerve.

MALAMUD, Iowa City.

VARIATIONS IN THE STRUCTURE OF THE CEREBRAL CORTEX. S. BLINKOV, Trudy inst. mozga **2**: 77, 1936.

Blinkov studied the basal part of the temporal lobe in ten human brains and asserts that this region does not correspond to any of the formations outlined by Brodmann or von Economo and Koskinas; they correspond only approximately to regions 36 and 20 and part of 38 of Brodmann and to regions TE_2, TF and TH and part of TG of von Economo and Koskinas. The basal region of the temporal lobe, according to Blinkov, is characterized by the presence of all the principal tectogenic layers, clear horizontal stratification of the upper three layers, inclusion in the fourth layer of cells from the third and dark coloring of the lower levels, due to the increased number of dark cells. The basal part of the temporal region presents a transition to the allocortex. This transition is expressed through its topography and structure. Blinkov distinguishes twelve fields in this region. The cortical surface of the area varies from 2,877 to 5,261 sq. mm., the average being 4,271 sq. mm. The oscillation coefficient is 56, while the coefficient of variation is 17 per cent. Extension of the cortex in the polar fields varies greatly. Extension of the cortex of the basal surface of the temporal lobe shows little difference in the two hemispheres.

NOTKIN, Poughkeepsie, N. Y.

Physiology and Biochemistry

A NOTE ON THE COURSE OF THE PROPRIOCEPTOR FIBRES FROM THE TONGUE. DONALD H. BARRON, Anat. Rec. **66**:11 (Aug.) 1936.

Action currents were investigated in the peripheral cut ends of the hypoglossal, lingual and chorda tympani nerves and the nerve of Wrisberg in cats, rats and rabbits. No activity was recorded from the hypoglossal nerve. Action currents were elicited in the lingual nerve by stretching, touching and burning. The response in case of the first two nerves resembled that from stimulation of stretch and touch receptors elsewhere. Tenth-normal hydrochloric acid, fortieth-normal sodium hydroxide and crystals of table salt applied to the anterior two thirds of the tongue evoked action currents in the chorda tympani nerve and the nerve of Wrisberg. Sugar and other sweet substances were ineffective.

RIOCH, Boston.

INTERPRETATION OF POTENTIALS LED FROM THE CERVICAL SYMPATHETIC GANGLION OF THE RABBBIT. GEORGE H. BISHOP, J. Cell. & Comp. Physiol. **8**:465 (Oct.) 1936.

The cervical sympathetic ganglion in the rabbit is long and thin. Its preganglionic myelinated fibers all synapse with postganglionic nonmyelinated fibers, and its blood supply is such that the ganglion can be dissected free for its whole length, thus permitting comparable records at various levels, with circulation adequate to maintain practically normal function. The results indicate that the potentials recorded from the ganglion are those of the fibers active under the lead and are not assignable to the cell bodies.

CHORNYAK, Pittsburgh.

ON THE MECHANISM OF ADAPTATION OF FREE ENDING TACTILE RECEPTORS IN FROG SKIN. MORTON A. RUBIN and BOLESLAUS J. SYROCKI, J. Cell. & Comp. Physiol. **9**:29 (Dec.) 1936.

There are two types of sensory nerve endings in the skin of the frog (Rana pipiens): (*a*) free epidermal endings, terminating between the epithelial cells, and

(*b*) subepidermal endings, terminating in bulblike structures. The free nerve endings serve as tactile receptors, and the subepidermal endings are probably general chemical and deep pressure receptors. The potassium in the frog's skin is concentrated in the epithelial cells, whereas it is practically absent from the corium. Adaptation is rapid in the free epidermal endings and slow in the subepidermal endings. Potassium in the frog's skin is favorably located to act in depressing the excitability of the free nerve endings. The hypothesis that adaptation is a property not of the sense organ (free nerve endings) but of its epithelial environment has been found to apply in the case of the frog's skin. The potassium hypothesis of adaptation is thus a general one, applying to both the frog and the mammalian skin.

CHORNYAK, Pittsburgh.

LACTIC ACID IN DOGFISH NERVE. WALTER S. ROOT, J. Cell. & Comp. Physiol. **9**:137 (Dec.) 1936.

The concentration of lactic acid in isolated nerves of the dogfish is related to the acid-base ratio of the tissue. Reports from many sources indicate that not only in isolated cells and tissue but in the animal body the lactic acid concentration is related to the acid-base ratio.

CHORNYAK, Pittsburgh.

THE DIRECTIVE INFLUENCE OF LIGHT UPON DROSOPHILA MELANOGASTER MEIG AND SOME OF ITS EYE MUTANTS. FRANK A. BROWN JR. and B. VINCENT HALL, J. Exper. Zoöl. **74**:205 (Oct.) 1936.

In order to analyze the functions of the optic apparatus of insects without using animals in which natural processes had been altered artificially, the directive effect of white and colored lights on the fruit fly Drosophila melanogaster Meig and three eye-mutant stocks was measured. The apparatus and methods were designed to yield results uncomplicated by the effect of light on the activity of the flies. Measurements of threshold of response showed that red full-eyed flies are the most responsive to all intensities of light, the white full-eyed flies somewhat less, the white bar-eyed flies considerably less and the red bar-eyed flies the least. If the facet number is assumed to be related directly to the surface area of the barred and full eyes, the logarithm of the threshold of response and the strength of the tropistic response appears to vary linearly with the facet number. Experiments with colored lights indicated that the presence of red pigment in the eye increases sensitivity to the shorter wavelengths. At the same time reduction of sensitivity to the longer wavelengths may occur. Bar-eyed flies are apparently relatively more responsive than full-eyed flies to red and blue-violet light and less responsive to blue-green light. Barring seems to have less effect on sensitivity of the unpigmented eye to ultraviolet light than on that of the pigmented eye.

WYMAN, Boston.

THE SUPERIORITY OF INTERMITTENT LIGHT IN THE ADAPTATION OF RETINAL PIGMENT. L. B. AREY and R. G. PRICE, J. Exper. Zoöl. **74**:303 (Oct.) 1936.

A small fresh water fish, the golden shiner (Abramis crysoleucas), was used. Animals were exposed to various conditions of light and darkness, and the eyes were examined histologically. It was found that for equal amounts of total illumination, intermittent light, of flash frequencies from 1 to 60 per minute, with alternate periods of dark of equal length, was more effective in producing a migratory response in the retinal pigment than stimulation with continuous light of equal strength. Intervals greater than thirty seconds were less effective than faster intermittencies. It appears that the effectiveness of intermittent light may be equal to, or more than, that of constant light of the same strength acting through twice as much net time. As a provisional, speculative hypothesis,

it is suggested that the higher efficiency of intermittent light in producing migration of pigment depends on the coasting of mobile pigment between flashes coupled with improved performance during illumination, due to the lowering of fatigue by interjection of brief periods of rest.

WYMAN, Boston.

ACTION OF ADRENALINE ON THE ELECTROMYOGRAM IN DECEREBRATE RIGIDITY. W. F. FLOYD and C. A. KEELE, J. Physiol. **87**:93P, 1936.

Electrical potentials were recorded from the quadriceps muscle of decerebrate cats by means of an Adrian concentric needle electrode, amplifier and cathode ray oscillograph unit. The potential changes characteristic of decerebrate rigidity were observed for a preliminary period, and if the preparation was found to be free from spontaneous fluctuations, the effects of intravenous injection of epinephrine in doses of from 0.2 to 0.4 mg. were determined. The results obtained in ten animals were: 1. A brief cessation of activity lasting for two or three seconds occurred about fifteen seconds after injection. 2. The original activity returned and in some cases was enhanced. 3. The activity declined gradually and finally ceased in from forty-five to ninety seconds after injection. 4. The activity returned gradually to the original level in from three to forty minutes after injection, in some cases returning and ceasing alternately before attaining the original level; the activity was subsequently enhanced in some cases.

ALPERS, Philadelphia.

CHANGES IN FUNCTION AND EXCITABILITY OF NERVE AND MUSCLE IN SITU IN THE FIRST STAGES AFTER LESION OF THE NERVE. J. RICHTER, Arch. f. d. ges. Physiol. **237**:319, 1936.

The brachial plexus was severed in white rats, and the rheobase, chronaxia and main utilization time (minimal time that the current needs to produce a full effect) were determined every three or four hours for from forty-eight to seventy-two hours. Six hours after the lesion of the plexus, the muscles show a slight shortening of the chronaxia and the main utilization time; from twenty-four to thirty-six hours after the lesion these values become distinctly increased. These changes are more marked after lesions with a blunt instrument, without complete severance of the nerves, than after severance with a sharp instrument. In the nerve the initial depression of these values is not definite, but eventually an increase in the chronaxia appears. The rheobase increases from about five to six hours later than the chronaxia. No isochronism of nerve and muscle was found under normal conditions.

SPIEGEL, Philadelphia.

INFLUENCE OF THE SYMPATHETIC CHAIN ON EXCITABILITY OF THE PHRENIC NERVE. E. T. VON BRÜCKE and K. YAMAGIWA, Arch. f. d. ges. Physiol. **237**:379, 1936.

The galvanic threshold of the fibers of the phrenic nerve originating in the fourth cervical segment was studied in rabbits by condenser discharges. Severance of the homolateral cervical portion of the sympathetic trunk induced in about one-half the cases an increase in the threshold of about 110 per cent. This increase started after a latent period of several minutes and reached its maximum in from one-quarter to one-half hour; it remained for hours at this level. Stimulation of the caudal, and sometimes the cranial, stump of the cervical portion of the sympathetic chain induced an increase in excitability of the phrenic nerve. Severance of the fifth and sixth cervical roots produced an initial decrease followed by a slight increase in the threshold of the phrenic nerve. After extirpation of the cervical portion of the sympathetic chain and the stellate and upper cervical ganglia, severance of the fifth and sixth cervical roots had no effect or induced only a decrease in the threshold. In order to explain these observations, it is assumed that fibers maintaining tonic excitability in the phrenic nerve enter from the

cervical portion of the sympathetic trunk by anastomoses with the phrenic nerve and thence, through the roots of the phrenic nerve, reach the cervical portion of the cord. Besides, there seem to exist in the roots of the phrenic nerve centripetal somatic fibers, the mechanical or electric stimulation of which decreases the threshold of the phrenic nerve.

SPIEGEL, Philadelphia.

FLACCID HEMIPLEGIA OF CEREBRAL ORIGIN. W. J. C. VERHAART, Psychiat. en neurol. bl. **41**:211 (March-April) 1937.

Verhaart examined the brain stem in serial sections in twenty-one cases of hemiplegia, among which were five instances of flaccid hemiplegia. He concludes that flaccid hemiplegia occurs when both the sensory and the pyramidal systems are destroyed. A lesion in the lateral thalamic nucleus and in the adjacent part of the internal capsule is the smallest focus which can produce flaccid hemiplegia. Interruption of the mesial fillet and the superior cerebellar peduncle plays an important rôle in this phenomenon. A flexed position of the paralyzed leg occurs when the frontal lobe or the frontopontile tract is involved. The lenticular nucleus has no influence on tonus, position or voluntary motion of the hemiplegic limbs.

LEWY, Philadelphia.

Neuropathology

ANGIOMA OF LEFT BRACHIUM PONTIS WITH ASSOCIATED ANEURYSMAL VARICES. CHARLES L. DALE and CYRIL B. COURVILLE, Bull. Los Angeles Neurol. Soc. **1**:88 (June) 1936.

A boy aged 9 years was seized suddenly with headache, stupor and vomiting, shortly after playing ball. Half an hour later he could not be aroused; the pupils were fixed; the pulse rate was 120, and the spinal fluid was extremely bloody. Death occurred after a few hours. He had recovered from a similar attack two years before. Necropsy revealed dilated, thin-walled veins in the left lateral fissure and along the left side of the pons. On section the left brachium pontis was observed to contain a large number of dilated veins, which had produced marked atrophy of the fibers of the middle peduncle and reduction in size of the left lobe of the cerebellum. No clinical evidence of cerebellar dysfunction had been noted during life.

MACKAY, Chicago.

THE PATHOLOGY OF "SWAYBACK": A CONGENITAL DEMYELINATING DISEASE OF LAMBS WITH AFFINITIES TO SCHILDER'S ENCEPHALITIS. J. R. M. INNES, Proc. Roy. Soc. Med. **29**:406 (Feb.) 1936.

Innes reports the clinical and anatomic findings associated with "Swayback," which occurs in new-born and young lambs in many parts of England and Wales. It is probable from published reports that the same condition has been observed in Peru, Sweden, Australia and South Africa. From 10 to 90 per cent of some flocks may be affected; in others, only a few.

Thirty-two affected lambs were studied from several outbreaks, their ages varying from twelve hours to twelve weeks. Some were allowed to die of the disease, while others were killed. Autopsies were performed on all animals within at least three hours after death, and a number of studies were made of the chemical and morphologic, as well as bacteriologic, changes in the blood before death. Cultures and tissues for virus studies were made from a variety of organs, and sections of various parts of the nervous system were made as a routine for microscopic examination. Two fetal and two young lambs were studied as controls.

The symptoms of the disease are: spastic paralysis, particularly of the hind-limbs; incoordination; blindness in some cases; a progressive course unassociated with fever and usually a fatal termination, caused in some instances by intercurrent infection. The characteristic lesion is diffuse symmetrical demyelinization of the cerebral white matter, varying from small foci in the central white matter to com-

plete demyelinization of the hemispheres. Axis-cylinders disappear at the same time or subsequent to the demyelinization. Gliosis, and often porencephalic areas, occur when the destruction is severe. Demyelinization is not present in the midbrain, brain stem or cerebellum. Secondary degeneration always occurs in the motor tracts of the cord. The nerve cells are relatively resistant.

The only abnormality revealed by study of the blood was a marked irregularity in size and shape of the red cells and rather frequent punctate basophilia. Repeated bacteriologic investigations of tissues and fluids by numerous cultural methods gave negative results. Emulsions of various organs and fluids from affected animals when injected in various ways into normal lambs failed to transmit the disease. From studies of the blood chemistry no abnormality was detected, save perhaps a reduction in blood phosphorus.

In many cases the disease begins in the fetus, and the possibility that the origin is always intra-uterine cannot be excluded. Innes discusses the possible causes of the disease and favors the view that it is due to a toxic substance carried by the ewe during pregnancy and for a short time after birth, having particularly strong affinity for the offspring. He thinks that the evidence is against the disease being hereditary or due to vitamin deficiency, lead poisoning or virus or bacterial infection.

McEachern, Montreal, Canada.

Histopathologic Changes Associated with Insulin Shock. H. Schmid, Ann. méd.-psychol. **94**:658, 1936.

Insulin shock is associated with profound disturbances in cerebral circulation. The blood, deprived of carbohydrate, cannot supply the nerve cells with the oxidation material most essential for life and function. Experimentally, insulin intoxication causes irreversible lesions in the cortex similar to those observed in postthrombotic softening. Postmortem study of brains of diabetic persons who have died as a result of an overdose of insulin has shown extreme dryness of the cerebral tissues, with intense neuroglial proliferation. In the case of a morphine addict who was cured by insulin, only to become addicted to its use, and who died as result of an accidental overdose, de Morsier observed widespread capillary hemorrhages with advanced perivascular gliosis. These changes may be regarded as the result of slowing of the circulation in the capillaries, with lack of oxidation in the tissues. The lesions in the brain are the same as those observed in cases of death resulting from artificial low atmospheric pressure. However, all the aforementioned changes hold true only in fatal insulin intoxication. In order to establish to what extent insulin treatment might cause lesions in the brain, Schmid submitted eleven rabbits to a series of daily insulin shocks followed by the administration of dextrose. The treatment was continued for three weeks; after the animals had been submitted to from two to twenty-eight shocks they were killed. The lesions in the brains of these animals were discrete. No changes were noted in the cells of the cerebral cortex except a slight degree of swelling of the cell bodies and hyperchromatosis of the processes. A glial reaction was evident and consisted mainly in marginal gliosis with swelling of the astrocytes and increased microglial activity. The myelin sheaths were intact throughout. The basal ganglia showed a distinct glial reaction, but changes in the nerve cells were discrete. The cerebellum showed discrete changes, which were confined almost exclusively to the Purkinje cell layer; the cells were pale and swollen but showed no decrease in number. The vascular changes in the brain were most conspicuous and consisted of capillary hyperemia.

Yakovlev, Waltham, Mass.

Clinicopathologic Study in a Case of Neurofibromatosis of the Neuraxis and the Extremities. G. Hoerner, Corino d'Andrade and Basow, Encéphale **31**:124, 1936.

The case is reported of a woman aged 21 with a typical history of acoustic neurinoma, with progressive vertigo, loss of auditory acuity, tinnitus and facial paresis. Examination showed, in addition, hypesthesia of the cornea, nystagmus,

vestibular hypo-excitability, bilateral papilledema, albuminocytologic dissociation of the cerebrospinal fluid, roentgenographic evidence of hypertension and destruction of one internal auditory meatus and widening of the other. There were small, unpigmented subcutaneous nodules. Biopsy showed a typical neurofibroma. The patient died after a two stage operation. Autopsy revealed multiple meningoblastomas of the fasciculated type, originating from the dura over the cerebral convexity and the spinal cord, and multiple neurinomas of the cranial and spinal roots, including one subpial nodule in the thoracic portion of the cord which accompanied a dorsal root and pushed the substance of the cord before it. In the cervicothoracic portion of the cord distinct glial proliferation with deposition of collagen fibers surrounded the central canal. In the upper thoracic region the central canal was replaced by a diffuse "gliomatous neoformation," in which were several ependymal canals. The cells showed no cilia or blepharoplasts. In the midthoracic region were several small, superposed cavities surrounded by glial tissue, recalling syringomyelia. The left sciatic nerve presented two neurofibromas. The pituitary gland showed an excess of eosinophilic cells. There was a persistent thymus. The ovaries were striking by the absence of graafian follicles. Only atretic cysts and rare luteal scars were present.

LIBER, New York.

ANATOMICOPATHOLOGIC STUDY OF ARACHNOIDITIS. P. VAN GEHUCHTEN, Rev. d'oto-neuro-opht. **14**:708 (Dec.) 1936.

The pathologic changes in a case of arachnoiditis caused by trauma are recorded. The case was classified as one of inflammation of the pia-arachnoid. Van Gehuchten thinks it logical to assume that chronic arachnoiditis evolves by passing through a stage of acute or subacute leptomeningitis.

DENNIS, San Diego, Calif.

OBLITERATION OF THE AQUEDUCT OF SYLVIUS IN INFLAMMATORY PROCESSES. L. BÉRIEL, Rev. d'oto-neuro-opht. **14**:720 (Dec.) 1936.

In a patient who had had cerebral symptoms since youth a syndrome of cerebral hypertension developed. Decompression gave temporary relief, but the patient became so infirm that he was placed in a hospital for incurable diseases. A diagnosis of lesion of the red nucleus was confirmed at autopsy. Complete cicatricial obliteration of the aqueduct of Sylvius was also observed. In such cases catheterization of the aqueduct offers no prospect of permanent relief, and means must be sought to restore the circulation of the cerebrospinal fluid by trepanation of the corpus callosum or by an opening in the region of the pineal gland.

DENNIS, San Diego, Calif.

LESIONS OF THE INFERIOR OLIVES IN DEMENTIA PARALYTICA. B. A. MOYANO, Rev. neurol. de Buenos Aires **1**:187 (Nov.-Dec.) 1936.

Moyano observed lesions in the inferior olives in twelve cases of dementia paralytica. The process is characterized especially by periaxial demyelinization of the fibers, with severe glial sclerosis and absence of degeneration of the ganglion cells. The changes in the olives explain the dysarthria that occurs in dementia paralytica.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

PSYCHOLOGIC MEDICINE AS PRACTICED BY THE QUACK. CHARLES A. RYMER and MARION REINHARDT RYMER, Am. J. Psychiat. **92**:695 (Nov.) 1935.

Methods of quacks who give lectures on popular phases of applied psychology have been studied by Rymer and Rymer. The qualities which characterize the successful quack of this type are: a gift for anecdote, skill in forceful speaking,

an understanding of the dramatic and a knowledge of the reactions of the audience. Those who patronize quacks are usually unhappy, neurotic persons in search of happiness, certainty and a simple solution of their problems. Many of the clients are drawn from the ranks of those who have had unfortunate experiences with physicians. Physicians contribute to the treasury of the charlatan in two ways: They encourage a general interest in science, which they do not satisfy, and they fail to take persons with neuroses seriously. Quackery of this type is considered socially undesirable, for it broadcasts dangerous misinformation about health, it arouses a false sense of security and it undermines confidence in the medical profession. The authors recommend a more complete study of the subject by psychiatric associations and suggest that cities refuse lecture permits to unqualified speakers on any phase of medicine. They also urge county medical societies to embark on an intensive program in the education of the public on the subject of mental and physical health.

DAVIDSON, Newark, N. J.

PSYCHIC TRAUMA IN THE ETIOLOGY OF GRAVES' DISEASE. ISRAEL BRAM, Am. J. Psychiat. **92**:1077 (March) 1936.

In reviewing the histories in 5,000 cases of exophthalmic goiter, Bram found a record of significant psychic trauma in 90 per cent. Shock and terror incident to accident and narrow escape from danger comprised the exciting factor in 35 per cent of the cases, while shock associated with the death of a loved one was represented in 32 per cent. Less frequent was trauma incident to surgical operation (7 per cent) and to pregnancy or the puerperium (4 per cent). Other factors were: worry over physical illness, sexual maladjustment, business worries and concern over studies. In 100 of the 5,000 cases focal infection appeared to be a significant precipitating factor, but even in this group Bram is inclined to look for undisclosed emotional maladjustments, assigning to the infection the rôle of increasing the patient's sensitiveness to the psychic trauma. Because of the importance of the psychic factor, he considers the higher cerebral centers to be implicated, directly or indirectly, in the pathogenesis of exophthalmic goiter. The type of person who is a potential candidate for hyperthyroidism may be described as an emotionally unstable young adult, with bright, sparkling eyes, heightened cerebration, vasomotor ataxia and an excitable heart.

DAVIDSON, Newark, N. J.

PROBLEMS OF CONVALESCENCE AND CHRONIC ILLNESS. H. FLANDERS DUNBAR, Am. J. Psychiat. **92**:1095 (March) 1936.

Emotional factors predispose to illness in four ways: 1. The tension of anxiety situations may directly render the patient sensitive to trauma, as, for example, proneness to accident in an emotionally disturbed automobile driver. 2. Physiologic changes, such as vascular spasm and excessive salivation, may modify physiologic processes. 3. Psychic factors may initiate a long chain of events, leading ultimately to physical problems: thus, a personality problem may be associated with frequency and expediency of bowel movements, which in turn may promote constipation, thus precipitating hemorrhoids eventually. 4. Chronic emotional stress may limit the adjustability of the organism and disturb its chance of regaining or maintaining a stable equilibrium.

In the clinical picture of organic disease the symptomatology is more devastating in persons with an excessive amount of unreleased anxiety. This plays a rôle in the tendency to relapse, for if the illness serves a psychically useful function, the patient has a powerful, albeit unconscious, reason for remaining ill. Consequently, if the underlying neurotic conflict is relieved, the patient can afford to relinquish the neurotic fragment of his sickness—often the exact part of the disease which is keeping him ill. Psychotherapy must therefore be considered an indispensable weapon in the management of the convalescent patient.

DAVIDSON, Newark, N. J.

THE NEYMANN-KOHLSTEDT TEST FOR INTROVERSION-EXTROVERSION AS APPLIED TO DELINQUENTS. M. J. PESCOR, Am. J. Psychiat. **92**:1137 (March) 1936.

Using the Neymann-Kohlstedt test on 1,000 inmates of a federal penitentiary, Pescor found a normal frequency distribution without any marked preponderance of introversion or extroversion. If, as the devisers of the test have suggested, the normal distribution is bimodal, it would appear that neutroverts are more likely to be sent to federal prisons than introverts or extroverts. However, a statistical analysis of the results of this survey raises serious doubts as to the reliability and validity of the Neymann-Kohlstedt test. Thus, correlation of the scores in the first half of the test with those in the second half produced a coefficient of reliability of only 0.19, suggesting that the test is by no means a uniform measure of the introversion-extroversion quality. Further study by retesting showed a reliability coefficient of 0.63, indicating that the test is sensitive to emotional factors, to transitory moods or to temporary psychic disturbances. When the 140 most extroverted persons were compared with the 140 most introverted subjects, a surprising similarity in the two groups was discovered. No significant differences were found in educational background, vocational status, age, body type or emotional stability. DAVIDSON, Newark, N. J.

ALLERGIC REACTIONS IN MENTAL DISEASES. JOSEPH A. BEAUCHEMIN, Am. J. Psychiat. **92**:1191 (March) 1936.

Using skin tests, Beauchemin found evidence of a definite allergic tendency in nearly all epileptic patients with psychosis. The reactions suggested that these patients suffered disturbances in the power of assimilation and digestion by the body tissues of proteins from fats, meats and cereals. Most manic patients gave positive responses to total adrenal substance, whereas this reaction occurred in only 8 per cent of persons with depressive psychoses. On the other hand, most of the latter patients gave positive reactions to adrenal cortex. Beauchemin interprets this as suggesting that in manic-depressive psychoses hyperfunction of the adrenal and pituitary glands may exert a stimulative effect on the gonads and thyroid. Of schizophrenic patients 40 per cent gave positive tests to thymic substance. These results were all significantly different from the reactions of normal persons with no psychosis used as a control group. DAVIDSON, Newark, N. J.

FUNCTIONAL CHANGES IN THE PATELLAR REFLEXES AS SEEN IN THE PSYCHOSES. EDWARD STRECKER and JOSEPH HUGHES, Am. J. Psychiat. **93**:547 (Nov.) 1936.

In a group of seventy-three psychotic patients Strecker and Hughes studied the intensity of the patellar reflex response by means of a mechanism which records the amount of swing of the ankle when the patellar tendon is struck. Reenforcement was secured by having the patient stretch between his hands a spring scale with a force of 4 Kg. In a group of normal subjects used as controls, the authors found that the greater the force of the stimulus to the knee the greater the response. In agitated and depressed patients the knee jerks were exaggerated; often a stimulus too light to effect any reaction in a normal person caused a response in a depressed psychotic patient. Patients with dementia praecox showed normal responses. Reenforcement usually increased the response, except when the original reaction was great; under such circumstances reenforcement was ineffective. When a depressed patient showed clinical improvement, the reflex response became less marked, approaching normal as the mental state became so. Strecker and Hughes suggest that as a result of the agitated depression many stimuli pour into the spinal cord from the higher cerebral centers, thus increasing the excitability of the neurons of the cord. DAVIDSON, Newark, N. J.

PSYCHIC FACTORS IN RHEUMATOID ARTHRITIS. GILES W. THOMAS, Am. J. Psychiat. **93**:693 (Nov.) 1936.

In all of thirty-one patients with rheumatoid (atrophic) arthritis Thomas found evidence of severe emotional disturbances, neuroses or characterologic abnormal-

ities. In each case the psychic factor preceded the arthritic changes, often by years. Although Thomas offers no hypothesis to account physiologically for the relationship between the emotional trauma and the organic changes in the joints, he cites several such theories found in the literature. Thus Smith (*New England J. Med.* **206**:211, 1932) expressed the belief that arthritis is a sequel to physiologic "depletion" and pointed out the effect of emotional trauma on metabolic balance and physiologic saturation. R. L. Jones is quoted as interpreting the relationship in terms of vasomotor changes. Thomas presents abstracts of the histories in twenty cases, in which the psychiatric factors preceding development of the arthritis are outlined. He concludes that "significant emotional disturbances precede the onset of rheumatoid arthritis, not only in a certain number, but in a surprisingly large proportion of cases—in this series, all of them."

DAVIDSON, Newark, N. J.

AN ATTEMPT TO DETERMINE THE CONSISTENCY OF JUDGMENTS REGARDING THE ADJUSTMENT STATUS OF CHILDREN EXAMINED BY A CHILD GUIDANCE CLINIC. MABEL A. CARBERRY, J. Juvenile Research **19**:75 (April) 1935.

Carberry attempts to evaluate the meaning of the reports of adjustment status of 305 children who had passed through the program of the California Bureau of Juvenile Research from July 1929 to July 1933. Four persons were asked to rate the present status of each child—the parent, the teacher, the local worker and the bureau worker. In few cases was it possible to obtain all four judgments. The majority of children were rated by three judges and a number by only two. Each judgment was made on a four point scale, which included the categories of status "adjusted," "partially adjusted," "unimproved" and "worse." For the 16 children with four raters the individual judges were in complete agreement 36.3 per cent of the time. For the 145 children with three judgments the raters were in complete agreement 58.5 per cent of the time. Of the 79 children with two judgments there was complete agreement in 72.3 per cent. The parent tended consistently to rate the child slightly higher than did any of the other raters. The teacher tended to rate the child lower than did either the local or the bureau worker. The local and the bureau worker were in agreement 80 per cent of the time. The largest percentage of children included in this study were rated as "partially adjusted." The next largest percentage were rated as "completely adjusted." The status of only a few was rated as "worse."

FERGUSON, Niagara Falls, N. Y.

THE INTELLIGENCE OF YOUNG MALE OFFENDERS. GEORGE E. HILL, J. Juvenile Research **20**:20 (Jan.) 1936.

This study concerns men who ranged in age from 16 to 26, with a median age on their admission to a reformatory of 19 years and 4 months. The results of the army Alpha test, which was administered to all inmates on admission, were secured in 1,285 of the latest 1,500 commitments. As measured by this test, this group should be classified with the dull normal group, though on the average they rated higher than a select group of 1,047 members of the army draft who were born in English-speaking countries. White offenders were significantly more intelligent than Negro offenders. Although the relationship between the type of crime and the intelligence is not clearcut or conclusive, there were interesting suggestions. Those committed for the two most frequent sexual offenses fell below the general average for the entire group, but three persons convicted of the offense of contributing to delinquency were high in mental ability. Extortion and confidence games were practiced by the more intelligent offenders. There was evidence that the average habitual offender is more intelligent than the first or occasional offender.

Among this group the more intelligent were more commonly unemployed. There is evidence that they were the less experienced and the less secure of

commercial and artisan workers. Low intelligence and retardation in school were commonly related in this group of boys. The boy of low intelligence apparently labors under distinct handicaps in school, as is shown by his failures and low achievement. The most significant fact which this study brings out in regard to the relationship between delinquency and intelligence is the association which seems to exist between success in school and mental ability. Apparently, among these boys the lad of low ability, the slow learner, had been placed under circumstances at school and given a type of training that made success improbable. That his failure may be regarded as one of the "causes" of his delinquency is within the realm of probability.

Though the elimination of failure in school could hardly be expected to eliminate juvenile delinquency, there is plenty of evidence that it would help. The slow-learning child in school is a prospective citizen. The schools must, and many of them are beginning to, adjust their programs to provide satisfying learning experiences for these children. FERGUSON, Niagara Falls, N. Y.

MENTAL-HYGIENE ASPECTS OF THE DAY NURSERY. ETHEL S. BEER, Ment. Hyg. **20**:41 (Jan.) 1936.

Many day-nurseries take care of children of working mothers only. These institutions are the only ones that can be relied on in an emergency to give adequate daytime care to otherwise neglected preschool children. In providing companionship with his contemporaries for the child, the day-nursery is preferable to a permanent institution, since it does not necessitate disruption of the family and removal of the child from his own home and provides an environment that is not entirely artificial. The day-nursery has unlimited opportunities to follow the child's growth and expansion; it can be of great benefit educationally and can help in the formation of desirable social and hygienic habits. It is frequently an agency for family case-work, giving advice and assistance and securing for families the help of various organizations. It can also be of tremendous influence in the neighborhood.

Stressing the welfare of the children instead of relief for working mothers as the main purpose of day-nurseries will create higher standards. Good results require proper surroundings, with efficient space, proper washing and toilet facilities, adequate furnishings and playground equipment essential for a well regulated, healthy daily program. Attention should be given to the general physical and mental condition of the children, but experimentation should be excluded; discipline and group organization should not suppress children or prevent their happiness.

The great responsibilitiy of training children in these formative years necessitates emphasis on the quality rather than the quantity of the work accomplished. Beer suggests training a small number as thoroughly as possible by maintaining high standards for the plant and personnel. DAVIDSON, Newark, N. J.

FREQUENCY OF ACTIVE TUBERCULOSIS IN A HOSPITAL FOR MENTAL DISEASES, WITH SPECIAL REFERENCE TO SCHIZOPHRENIA. DAVID ROTHSCHILD and MORRIS L. SHARP, New England J. Med. **214**:929 (May 7) 1936.

There is a widespread belief that patients with schizophrenia are especially likely to acquire active tuberculosis. A survey was made of the deaths from tuberculosis at the Foxboro State Hospital from 1920 to 1934. Although for 63.7 per cent of the patients in the whole tuberculosis group there was a diagnosis of schizophrenia, an analysis of the data showed that the incidence of active infection for patients with dementia praecox did not differ greatly from that of patients with all other psychoses considered as a group.

Patients with schizophrenia remain on an average for a considerably longer time in the hospital than most other patients, and thus the period is longer during which tuberculous disease may develop.

In view of these considerations there does not seem to be a great difference between schizophrenia and other types of psychosis with respect to the frequency

of active tuberculosis. Tuberculosis tends to occur in patients who show the least active tendency to recover mentally and who thus represent the most outspoken examples of a decompensating psychosis within the schizophrenic group. It is probable that the increased susceptibility of patients with schizophrenia to tuberculosis is due to a combination of two factors: unhygienic modes of life with prolonged hospitalization, on the one hand, and a lowered resistance, which is correlated with decompensating mental reactions, on the other.

MOORE, Boston.

A CLINICAL STUDY OF LEARNING IN THE COURSE OF A PSYCHOANALYTIC TREATMENT. THOMAS M. FRENCH, Psychoanalyt. Quart. **5**:148, 1936.

French presents a clinical study to illustrate Alexander's thesis that the most fundamental process in psychoanalysis is an integrative one which achieves its therapeutic effect by bringing under the conscious control of the ego impulses that formerly had been left to unconscious elaboration and synthesis independent of the central core of the personality. The three factors—emotional abreaction, recovery of repressed infantile memories and intellectual insight—are only partial aspects of the more comprehensive reintegrating process.

French's method is to compare dreams and fantasies produced during three weeks of analytic treatment. The patient's problem at this point turned about his desire to enter into a libidinal relationship with the analyst, hindered by his fear of the aggressive impulses toward the analyst that such a relationship would entail; i. e., the problem was one of ambivalence toward his father.

The patient's first dream occurred as a result of obtaining money from his mother. Because of her real interest in him, the patient was able to prevent an acute attack of sadism or masochism toward the analyst by withdrawing his energy from the infantile intrapsychic conflicts, in the hope that his mother's present interest would make up for his infantile deprivations and therefore relieve the pain of his conflict about his father. He therefore tried to make the analyst a mother, but the rivalry with his own mother came to the fore, so that he had the same problem of ambivalence with which he started, and he was unable to get love from the analyst without having hostile feelings toward him. He became enraged at this frustration, and after expressing his rage and fury, compounded of envy of and rivalry with the analyst and fear of castration for his aggression, he gave grudging acknowledgment in a dream that the analyst's interpretation was correct: he was willing to accept an unpleasant fact about himself (i. e., his passive homosexual wish for the analyst) because he realized it was not a real castration. Thus, he had learned to differentiate between the analytic situation in which rage and envy can be expressed without punishment and other situations in which it cannot, particularly the situation of his childhood. By reassuring himself that the analyst was friendly, he could withdraw some of the energy from the conflict between his love for and envy of the analyst to use in cooperating with the analyst in the investigation of his unconscious mechanisms. In so doing, he accepted the unpleasant insight in place of the castration which he feared.

PEARSON, Philadelphia.

TEMPERAMENT TESTS IN CLINICAL PRACTICE. RAYMOND B. CATTELL, Brit. J. M. Psychol. **16**:43, 1936.

Temperament, Cattell observes, is important in the evaluation or planning of behavior. He calls temperament that which "through experiment . . . emerges from the noncognitive side of personality," "runs through all behavior" and "is predominantly inborn." Previous statistical studies of late adolescents led him to group together certain traits and their opposites which constitute what he calls "surgent" and "desurgent" temperaments. These are related to a factor "c" in the personality. Another smaller group of traits (related to a factor "a") modifies the larger group "c" in varying degrees, he believes, to produce the typical intro-

vert or extrovert. Present tests of temperament are not satisfactory, he finds, since they are not based on a clear concept of temperament. He discovered that tests for fluency of association ("f") and for perseveration ("p") could be correlated to some degree with estimates of "c" and "a," respectively.

ALLEN, Philadelphia.

ON CO-EDUCATION. LAURA HUTTON, Brit. J. M. Psychol. **16**:62, 1936.

Largely on theoretical grounds, Hutton concludes that coeducational schools with male teachers are probably desirable. "The girl is relatively more than the boy controlled by her super-ego, the boy more by his reality-testing ego. The girl must at all costs please: the boy can afford not to. Co-education should be able to do something to modify the extremes of these attitudes, enabling the girl to reduce some of her anxiety in the easier company of masters and boys, and stimulating the boy to emulate the super-ego achievements of girls."

ALLEN, Philadelphia.

THE STRAIN OF SCHOOL LIFE ON GIRLS DURING THE EARLY MENSTRUAL PERIOD. D. J. GAIR JOHNSTON, Brit. M. J. **2**:892 (Nov. 9) 1935.

This study is a condensed account of an inquiry carried out at the request of an authority on education to determine the effect of the strain of school life on the physical welfare of girls during the somewhat critical period of the early menstrual years. The physical development of girls between the twelfth and the fifteenth year is much more rapid than that of boys. In this period sexual development, with all its attendant disturbances, is active. Girls are more conscientious; hence, this rapid physical and sexual growth coincides with a strenuous educational effort. Their standard of fitness is less than that of boys and depreciated more during the period of this study. The investigation showed conclusively that home work required a greater expenditure of energy by girls, and, therefore, greater care ought to be exercised in guarding their health.

BECK, Buffalo.

THE PSYCHOLOGY OF CARICATURE. ERNST KRIS, Internat. J. Psycho-Analysis **17**:2 (July) 1936.

The word "caricature" in its Italian and French meanings conveys the idea of charging or overcharging. Thus, the human face may have a single feature accentuated so that the representation is overcharged with it. The aggressive nature of all caricature, which seems to condition its mechanism, is mentioned in its earliest definitions. It serves the purpose of unmasking another person familiar to one in order to degrade him. There is a relationship between dreams and caricature, as caricature is the graphic form of wit. As in wit and dreams, so caricature owes its nature to operation of the primary process found in the child. This explains why caricatures look somewhat like children's drawings. The distortion in image represents a distortion of the original. Behind the comic gesture of the caricature there is a psychologic motif of annihilation.

Wherever caricature develops one finds development of effigy magic. As one makes an effigy of the person whom one wants to destroy by magic, so with caricature one aims to accomplish the same destructive effect. A root of caricature is punishment to a culprit beyond reach.

KASANIN, Chicago.

DOMINANT IDEAS AND THEIR RELATION TO MORBID CRAVINGS. THERESA BENEDEK, Internat. J. Psycho-Analysis **17**:40 (Jan.) 1936.

Addiction to the use of drugs is a secondary illness. The primary illness is usually a depression which has different causes in different persons. The analysis and genesis of the structure of the primary depression give an idea of the foundation of the craving for drugs. In an unmarried woman aged 26 it was possible to

obtain an unusually clear view of the addiction as a secondary illness, a defense against the initial depression created by the primary morbid process. The driving force behind the complicated addiction was the idea which was conscious for the patient, that she did not want to have a woman's body. This idea emerged when she was 15½ years old, with such overwhelming force that it destroyed her adjustment to life. After shocking disappointments in the father and in a father substitute, she rejected the female body in its entirety, with all its visible feminine attitudes, on the ground that all this served the man as a sexual object. However, she continued always to seek refuge with men, because she was filled with pathologic mistrust and hatred toward women. This paranoid hate of women inspired her rage against her own body.

Before closer examination of the symptom represented in the idea "I do not want to have the body of a woman," there is described the case of a girl aged 21 with the same idea and the same reaction of refusal of food, in order that she should not become like her mother, whom she hated and killed in her own body. Psychoanalysis in both cases showed that this idea was the result of an instinctual conflict which arose from oral anxiety and oral hatred toward the mother and by way of identification rages against the subject's body, evoking a paranoid illness with a reversal of aggression against the self.

This circumscribed idea is dominant and is the result of psychotic regression. It is a monosymptomatic psychosis. The dominant idea, which forbids the person to eat, releases further conflict tensions. The attempt to master these tensions first takes shape as a depression, with concomitant heightening of instinctual oral tension. The resolution of the tension, so produced, can no longer be entirely accomplished by endopsychic means; hence the release of addiction in the form of an illness with two phases.

The case under discussion is to be regarded as one merely of a specific type of addiction. Independently of the nature of the neurotic or the psychotic process which maintains the primary depression, the general mechanism of addiction is to make repeated attempts to resolve inward conflict by means of incorporation. A final adjustment cannot be achieved, since the forces in the ego have already been exhausted. The discharge of the emotional tension arising out of the primary instinctual conflict, or due to the primary symptom, takes place autoplastically, an attempt being made to effect an alteration in the ego by means of the drug which is taken from the external world and incorporated in the ego.

KASANIN, Chicago.

SOME RECENT INVESTIGATIONS INTO THE HAEMATOLOGY OF THE PSYCHOSES. H. C. BECCLE, J. Ment. Sc. **81**:840 (Oct.) 1935.

Beccle made a study of toxic and sudanophilic granules in the blood smears of twenty patients who were acutely ill with mental disease, ten patients with chronic disease and fifteen normal persons used as controls. He states that the upper limit of normal variation consists in a count of 9 per cent for the toxic and 5 per cent for the sudanophilic granules. In the acute psychoses the counts for the toxic and the sudanophilic granules are much higher than the normal, varying with the intensity of the psychosis. With clinical improvement, the high granule counts drop, possibly owing to general detoxication of the patient. In spite of the small number of patients studied, Beccle believes there is a definite correlation between the granule counts and the severity of the illness.

KASANIN, Chicago.

MESCALIN AND DEPERSONALIZATION: THERAPEUTIC EXPERIMENTS. E. GUTTMANN and W. S. MACLAY, J. Neurol. & Psychopath. **16**:193 (Jan.) 1936.

Depersonalization, a syndrome occurring in various psychic disturbances, can be analyzed into feelings of unreality related to the patient's own personality and those relating to the outer world ("derealization"). Experimentally, similar phenomena accompanied by changes in mood have been produced by mescaline

intoxication. The state following the intoxication has been known to enhance the patient's insight into his psychic life. These observations led Guttmann and Maclay to use the drug as a psychotherapeutic method in eleven cases of states of depersonalization. Small quantities of the drug (from 0.1 to 0.2 Gm., by mouth) were preferred, as larger doses produce vegetative symptoms, disturbances in perception and stereotyped pictures of an exogenous reaction type. The following results are summarized: (1) mescaline may remove symptoms of depersonalization only so far as they are related to the outer world ("derealization"); (2) improvements were noted in patients of the manic-depressive group, namely, in four persons with endogenous depression; (3) cyclothymic persons tend to react to small doses of the drug with reactions of their own endogenous type (homonymous), whereas patients with schizoid personalities show heteronymous reactions, and (4) for patients who fail to show permanent improvement the method may be useful as an adjuvant to psychotherapy.

N. MALAMUD, Ann Arbor, Mich.

HEAT REGULATION IN DEMENTIA PRAECOX: REACTIONS OF PATIENTS WITH DEMENTIA PRAECOX TO COLD. ISIDORE FINKELMAN and W. MARY STEPHENS, J. Neurol. & Psychopath. **16**:321 (April) 1936.

Chemical regulation of temperature consists of a reflex increase in heat production in response to a low external temperature. Physical regulation is an adjustment of the heat loss of the body on exposure to ordinary environmental changes in temperature. The efficiency of the former was tested in fifty female patients with hebephrenic dementia praecox. The patients were exposed to a temperature of about 60 F., and their oxygen consumption rate was noted before, during and after exposure. As controls, twenty-six subjects with no psychosis and twelve patients with chronic encephalitis were used. The schizophrenic patients reacted to cold as a group with a lower production of heat and a greater drop in temperature than the normal persons. Moreover, the continued increased metabolic response for some time after exposure which was observed in normal persons was not elicited in patients with dementia praecox. The latter also failed to show the reactive hyperemia normally occurring on removal from the cold bath; instead there was vasoconstriction. The respiratory shock and shivering observed in normal persons on exposure to cold were diminished or absent in the schizophrenic patients. Changes in blood sugar were not found in any of the cases, suggesting that epinephrine does not act as a calorigenic agent on exposure to cold. Finkelman and Stephens conclude that there is inadequacy in regulation of heat in schizophrenia and relate this to possible disturbances in the physiologic activity of the hypothalamus. Reactions elicited in schizophrenic patients were similarly observed in patients with postencephalitis. This would support the hypothesis of disturbances in the hypothalamus, since pathologic changes are frequently encountered in that region in cases of postencephalitic Parkinsonism.

N. MALAMUD, Ann Arbor, Mich.

TUBERCULOSIS AND DEMENTIA PRAECOX. J. BEERENS, Ann. méd.-psychol. **94**:1 (June) 1936.

Statistical studies fail to yield irrefutable proof of the special prevalence of tuberculosis among patients with dementia praecox as compared with those having other types of psychoses. Beerens reports the results of laboratory researches on this subject. Guinea-pigs sensitized to tuberculosis were inoculated with the blood and spinal fluid from patients with dementia praecox who had tuberculosis. The inoculations were carried out twice a week for from five to six weeks. The animals were given tuberculin tests and at the end of two months were killed; the lymph nodes, spleen and lungs were crushed, and the product so obtained was inoculated into another series of guinea-pigs, which were then treated with an injection of an acetone extract of tubercle bacilli. A portion of the crushed organs was used for cultures. If the culture proved sterile, the inoculations were repeated until positive cultures were obtained. For identification of the cultures

and study of their pathogenic power, inoculations were made into various laboratory animals (the guinea-pig, rabbit and chicken). The results of this last test alone were taken as proof of the presence or absence of tuberculous virus.

Of twelve patients whose blood and spinal fluid were so studied, all proved to give negative reactions. Beerens' results are in agreement with those obtained with the same method by Claude and Coste and by Beck. The inoculation of postmortem cerebral tissue from patients with dementia praecox made by Barahoma and Beck also yielded negative results. Beck failed to find evidence of tuberculous antigen and antibodies in the cerebrospinal fluid of patients with dementia praecox. In view of all these normal laboratory findings, it is difficult to accept the tuberculous etiology of dementia praecox. YAKOVLEV, Waltham, Mass.

THE MENTALLY DISEASED IN EUROPE. H. BERSOT, Ann. méd.-psychol. **94**:88 (June 3) 1936.

In the countries of Europe west of Soviet Russia and northwest of Rumania and Serbia, there were treated during one year 553,622 patients with mental disease, 48.7 per cent of whom were men and 51.3 per cent women. Thus, in Europe mental disease among women is slightly more frequent than among men. This, however, is only relatively true. In Lithuania, Portugal, Poland, Iceland, Finland, Italy, Norway, Austria, Belgium and Sweden there are more men than women with mental disease. The greatest proportion in the population is found in England and Switzerland (40 per 10,000); next come Belgium, Holland and the Scandinavian countries (from 25 to 40 per 10,000). Austria, Czechoslovakia and the Latin countries follow. Portugal and the countries of eastern Europe show the lowest incidence of mental disease in the total population. Of the total number of the mentally ill discussed here, 133,606 patients were newly admitted during one year, 69,232 of whom were men and 64,274 women. The male population of institutions is more changing than the female, women tending to remain longer. The number of patients admitted varied greatly from one country to another. In Lithuania 50 per cent of patients treated during the year were new admissions; in Poland, Austria, Switzerland, Czechoslovakia, Finland and Germany, more than 40 per cent, and in Latvia, 31 per cent. The number of new admissions was below 20 per cent in Holland, England and Ireland. In other words, the countries of eastern Europe show the greatest proportion of new admissions; those of central Europe occupy an intermediate position, and those of northern Europe show the lowest proportion of new admissions. In almost all countries the figures for discharges are slightly below those for admissions. There is, therefore, a general tendency toward progressive increase of population in institutions. Almost everywhere, the number of men discharged exceeds that of women. Only in Norway is this relation reversed, while in Sweden, England and Ireland the numbers of discharged male and female patients are about equal.

As to the incidence of various clinical categories of mental illness, Bersot cites his figures for the manic-depressive and syphilitic psychoses. In a total of 105,077 first admissions, for thirteen countries for which sufficiently complete statistical data were offered, there were 18,383 cases of manic-depressive psychosis, i.e., 17.5 per cent. The number of women with this psychosis prevailed—62 per cent (11,861) women and 28 per cent (7,021) men. The prevalence of women is found in all countries and shows nearly the same proportion except in Lithuania, where the relation between women and men reversed. The frequency of maniac-depressive psychosis was highest in France—27 per cent of patients admitted, 21 per cent of whom were men and 32 per cent women. The difference between the sexes was greatest in Italy (70 per cent men and 30 per cent women). Switzerland, Hungary and Lithuania have scarcely 4 per cent of patients with manic-depressive psychoses among their admissions. Statistics suggest that Latins and Scandinavians show a greater predisposition to manic-depressive psychosis than Germans and Slavs. It is possible that factors other than race, e.g., the psychiatric point of view in diagnosis, play a rôle. As to psychoses due to syphilis, in a total of 105,077 admissions there were 7,458 cases (7.1 per cent), with distinct prevalence

among men (74 per cent). Hungary shows the highest relative percentage of patients with syphilitic psychoses (14 per cent of all admissions). Then follow Latvia and Poland (10 per cent). Esthonia, Czechoslovakia (from 7 to 8 per cent), Austria, France and Italy have about 6 per cent of patients with syphilitic psychoses.

YAKOVLEV, Waltham, Mass.

A NEW REACTION OF THE PITUITARY APPLICABLE IN CASES OF MANIC-DEPRESSIVE PSYCHOSIS. X. ABÉLY, P. ABÉLY, COULÉON and COULÉON, Ann. méd.-psychol. (pt. 1) **94**:113, 1935.

The authors studied Zondek's "intermedin reaction" in the urine of manic-depressive patients. The test consists in treating an isolated scale of carp (Carassius vulgaris) for two or three minutes with the extract of morning urine of the patient and observing under the microscope the reaction of the melanophores in the scale. The reaction was nearly always positive during the manic phase of manic-depressive psychoses and was especially strong at the beginning of the manic excitation. The reaction is always negative in normal persons and in cases of psychosis other than the manic-depressive type. It may become negative in manic-depressive patients during intercurrent physical disease. In one patient with frequent alternation of the manic-depressive phases with a short normal interval, the reaction was positive during the manic phase and negative during the interval.

YAKOVLEV, Palmer, Mass.

DISTURBANCES IN GASTRIC MOTILITY IN CATATONIC SYNDROMES. P. TOMESCO, Encéphale **31**:212, 1936.

Gastrograms were taken in normal persons and in catatonic patients. In the normal person when at rest the gastric contractions last from fifty to sixty seconds each and produce displacement of from 4 to 5 cm. on the tracing. When the subject witnesses another person consume an appetizing meal, the contractions become irregular after a delay of one hundred seconds and increase in intensity and frequency. Three hundred seconds after the beginning of the meal, the excitation has reached its maximum. The contractions last for from twenty-five to thirty seconds. They produce an average displacement of 8 cm. When a catatonic patient is at rest, the contractions are regular but briefer than normal—thirty seconds. Their amplitude (2.5 cm.) is diminished. The heart beats, which are visible in the normal gastrogram, are weaker in the catatonic person and are not visible on the gastrogram. Two hundred seconds after the beginning of a meal eaten in the presence of the patient, the contractions are decreased and disappear almost completely, with occasionally an isolated contraction of usual amplitude. Results of this sort were obtained in many cases. In certain instances the sight of taking food does not inhibit the contractions, but it never increases them. Tomesco concludes that this gastric negativism is probably of cortical origin. The vagus innervation is inhibited at the moment it is normally excited. Negativism is not a psychic attitude alone. The patient refuses to eat not only because he wishes to do so but because his digestive apparatus is physiologically abnormal. These observations lead one to think that the same mechanism is at work in other forms of catatonic negativism. Verbal negativism is probably due not only to refusal to talk but to some physiologic change in the organs of phonation. Refusal to urinate is due in part to contracture of the sphincters. The therapeutic conclusion is that in order to affect the negativism an attempt must be made to influence the abnormal physiologic phenomena which accompany and perhaps amplify it.

LIBER, New York.

THE STIGMATIZED LAY SISTER MAGDELENA LORGER, OF OFFHEIM. CARL HEILER, Arch. f. Psychiat. **104**:435 (Dec.) 1935.

Anna Margareta Lorger, who was born in 1734 and entered a Dominican convent under the name of Magdelena in 1767, first began to show signs of ill

health in 1775, at the age of 41. The most important symptoms were vomiting, with a certain amount of hematemesis, and what seems to have been hysterical paralysis of the lower limbs. Five years later she began to show the stigmas which attracted the attention of her contemporaries. On her hands and feet appeared wounds simulating those of Christ—on her left side the bleeding reminiscent of the lance wounds, on her back the whip lashes and on her forehead marks of the crown of thorns. These bled and at times became purulent. Statements of observers were to the effect that frequently the stigmas disappeared, to reappear again without any known cause. It seems that they were most marked on Fridays, particularly on Easter Friday. In addition, she frequently lapsed into states of "ecstasy and visions." During these, she claimed to see angels and saints in her room, had convulsive movements and talked in a peculiar fashion. Further claims were that for a long period she ate little and had no evacuation of the bowels. In addition, she was said to have healed a number of incurable diseases by praying for or placing her hands on the patients. A short time after these signs were first noticed, a number of investigations were made both by the church and by civil authorities to ascertain the nature of the occurrences. It is of interest that one of the physicians appointed by the civil government regarded the whole picture as a combination of malingering and mental disease. He stated that no proof was found of the efficacy of her healing powers and that the absence of bowel movements was a falsification. Another physician, however, who examined her in association with some of the clergy, made an equally positive statement to the effect that all these claims were well founded. Both agreed on the presence of the other stigmas.

Heiler discusses these findings in relationship to present day theories of somatic symptoms in hysteria. He is of the opinion that the bleeding and other features of the stigmas are compatible with the vasomotor disturbances one finds in hysterical patients.

MALAMUD, Iowa City.

DELUSIONAL FORMATIONS IN EPILEPSY. HANS W. GRUHLE, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:395 (Jan.) 1936.

Gruhle notes that delusional formation during psychotic episodes is not unusual in epilepetic patients. The problem of persistent or chronic psychoses in idiopathic epilepsy is particularly emphasized. Gruhle found eight patients with chronic paranoid psychoses among ninety-two institutionalized epileptic persons (8.7 per cent). In one case the psychosis preceded the epilepsy. In the others the psychosis came on after the patient had had repeated epileptic attacks for a number of years. The delusional formations were usually simple, and the mental content was not complicated. Bizarre, fantastic delusional formations, such as are seen in paraphrenia, were not encountered in this series. The trend reactions were not always evident, and the patients frequently did not discuss the abnormal mental content spontaneously. The delusions became manifest suddenly, during periods of emotional upset. Careful questioning, however, in all cases showed that the patients all clung tenaciously to their delusions, which in most cases were simple ideas of persecution and reference. There was nothing characteristic and constant in the mental content, and the delusions could in no way be distinguished from the usual trend reactions of patents with schizophrenia. Gruhle insists that the paranoid syndrome in these cases was in the nature of symptomatic schizophrenia. Epilepsy can be the cause of such a schizophrenic reaction. He is inclined to accept the hypothesis that such a delusional formation indicates the probability of the existence of endogenous toxins. He denies that in these cases there is a fortuitous combination of two different diseases.

SAVITSKY, New York.

MINERAL CONSTITUENTS OF THE BLOOD OF NEUROTIC PATIENTS. A. PETRUNKINA, S. MINKER-BOGDANOVA, U. POVARINSKY and S. POVARINSKAYA, Arch. biol. naouk. **40**:213, 1935.

The authors investigated the mineral composition of the blood in a number of neurotic patients and compared the findings with those obtained in normal persons.

They found that the mineral content of the blood in neurotic patients fluctuates within wide limits. The fluctuation of a single element is more pronounced in neurotic than in normal persons. The authors observed a correlation between the state of the nervous system and the sodium content of the blood. In the "inhibitory" type of patients the average sodium concentration of the blood is lower than that in normal persons. The relation of the various minerals to each other is not the same in neurotic as in normal subjects. Of particular interest are the lowered calcium and magnesium contents of the blood in the "inhibitory" type of neurotic subjects.

NOTKIN, Poughkeepsie, N. Y.

Meninges and Blood Vessels

EARLY OCULAR COMPLICATIONS OF EPIDEMIC MENINGITIS. N. K. LAZAR, Arch. Ophth. **16**:847 (Nov.) 1936.

Ocular complications in epidemic meningitis are rare. Two major complications have been observed, namely, endophthalmitis and paresis of the external rectus muscles. Endophthalmitis was not influenced by the use of antitoxin or foreign proteins.

SPAETH, Philadelphia.

VASCULAR LESIONS IN THE REGION OF THE PONS AND PEDUNCLE: THEIR PATHOGENESIS. KARL STERN, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:497 (April) 1935.

The tegmentum of the pons and the cerebral peduncles are rarely involved by vascular disease. Forty-five cases of vascular lesion in the ventral part of the pons, regardless of etiology, were studied. Serial sections were made in only five cases. In most cases multiple small lesions were observed, especially in the region of the pontile nuclei and the gray matter between them. No electivity of injury to tissue was noted. Small glial foci involving the pontile nuclei and the pyramidal tracts were seen in the small or at the margins of the large lesions. Typical areas of softening were seen in only one case. État criblé was rare. The ventrolateral part of the pons is singularly free from vascular lesions. The paramedian and dorsolateral areas are especially involved. These areas are supplied by long central arteries, while the rest of the pons is supplied by short peripheral vessels. Hemorrhage occurs most often from the paramedian arteries in the pons. Bleeding from vessels is more frequent in the more dorsal part of the brain stem. Pontile bleeding is relatively rare. Hemorrhage near the tegmen is often gross and usually has a fountain-like appearance, as compared with bleeding at the base of the pons, which is usually diffuse and infiltrates the tissues. Bleeding in the base of the pons rarely ruptures into the subarachnoid space. The more dorsally placed apoplexies, however, not infrequently rupture into the fourth ventricle. Sites of predilection for pontile bleeding are about the same as those for softening. Stern studied the vessels of the brain stem of three hundred brains and observed no rule regarding the distribution of arteriosclerotic plaques along the main vessels and branches of the basilar and posterior cerebral arteries. He was unable to corroborate the generalization which Schwartz made for the carotid arteries and their branches—that the vessels which lie in the direction of flow of the larger vessels become more readily affected with arteriosclerosis. Stern studied only the vertebral and basilar arteries and their branches. Most of the vessels involved in the series studied branched from the basilar arteries at right or acute angles. These pontile vessels differ from the more commonly affected branches of the middle cerebral artery in the numerous extracerebral anastomoses between the vessels of the same and those of the opposite side. They divide a number of times before they enter the cerebral substance. Extracerebral anastomoses with branches of the posterior cerebral artery are also present.

The same type of extracerebral anastomoses is seen in the blood supply to the quadrigeminate bodies. The posterior quadrigeminate bodies are supplied by

three arteries from the medial branch of the superior cerebellar artery. One of these branches goes to the most dorsal part of the posterior quadrigeminate body; the second, to its lateral aspect, and the third, to its most caudal part. The anterior quadrigeminate bodies are supplied by branches of the posterior cerebral arteries.

The paramedian vessels of the pons are of constant caliber from the point where they branch from the basilar artery to their entrance into the cerebral substance. Extracerebral anastomoses are not present. These vessels supply a larger area of the brain stem than the more peripheral vessels. Softenings are more liable to occur in parts of the brain where each vessel supplies a relatively extensive area. The regions of the sixth, fourth and third nuclei are relatively resistant and are rarely affected by vascular lesions, because they receive their blood supply from two sources. Hypertension was the etiologic factor in most cases. In the others the cause was vascular syphilis. Four cases of hematogenous malignant metastases were observed in this series. The great rarity of emboli in the region of the brain stem is emphasized. The region of the base of the pons is particularly affected in the form of arterial hypertension in which the spinal pressure is also increased.

SAVITSKY, New York.

OPTOCHIASMATIC ARACHNOIDITIS. J. A. BARRÉ and J. MASSON, Rev. d'oto-neuro-opht. **14**:739 (Dec.) 1936.

On the basis of personal observations, Barré and Masson believe that neither ocular signs alone nor the evolution of the process permits a diagnosis of optochiasmatic arachnoiditis when the condition is strictly limited to the optochiasmatic region. There are numerous unanswered questions relative to arachnoiditis, such as whether it is primary or secondary, where the blood vessels in the inflamed arachnoid originate and the causes of exacerbations and regressions. There is also no agreement on the anatomic details of the normal arachnoid. Because operative intervention on neighboring structures in which considerable blood is lost results in relief of arachnoiditis, Barré and Masson are inclined to believe that arachnoiditis is secondary to a circulatory disorder. The analogy to the results of treatment of retrobulbar neuritis is striking. The same considerations apply to spinal arachnoiditis.

DENNIS, San Diego, Calif.

Diseases of the Brain

MULTIPLE INCIDENCE OF MONGOLISM IN THE SAME FAMILY. WILLIAM J. JOHNSON, Am. J. Psychiat. **93**:533 (Nov.) 1936.

Mongolism in twins is rare; the condition is also rare in the Negro race, and it is unusual to find two mongols in the same generation of a family. Although instances of all these have been reported, the number is small. To this scanty collection Johnson adds cases of mongolism in three pairs of persons. The first case is that of mongolian idiocy in a middle-aged woman, whose brother (a twin) had dementia praecox. These patients were born of the eleventh and last pregnancy of a mother aged 41. The second pair were a Negro boy aged 16 and his sister aged 7. Both were mongolian idiots, the boy being born of the fifth and the girl of the ninth pregnancy. The third instance was that of a boy aged 8, the first-born in the family, and a sister aged 4, the second-born; both were mongolian imbeciles.

DAVIDSON, Newark, N. J.

OTOGENOUS ABSCESS OF THE PARIETAL LOBE. CYRIL B. COURVILLE and J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **1**:65 (June) 1936.

Two cases of abscess of the parietal lobe secondary to homolateral otitis media are reported. In the first case a woman aged 60, who had had recurrent left hemiplegia, presented deep coma, deviation of the eyes to the left, irregularity of the pupils, with the left larger than the right, flaccid left hemiplegia and a Babinski

reaction bilaterally. The spinal fluid was opalescent, slightly xanthochromic and under elevated pressure. Autopsy revealed bronchopneumonia bilaterally, mucopurulent exudate in the left middle ear and an encapsulated abscess just under the cortex of the left parietal lobe. A thick, greenish exudate was present in the leptomeninges over the abscess. A second, fresh abscess was observed anterior to and continuous with the first. Streptococci were cultured from both the ear and the abscess.

In the second case, a Negro boy aged 4, who had always been mentally retarded, was suddenly paralyzed in the right arm, after which convulsions occurred in the right extremities and soon became generalized. The spinal fluid was under a pressure of 400 mm. of water and contained 44 cells per cubic millimeter. Signs of meningeal irritation followed. Autopsy revealed congenital pulmonary stenosis, pus in both middle ears and a large abscess in the left superior parietal lobule, which was poorly encapsulated and superficial. Streptococci were cultured from both the ears and the abscess.

Courville and Nielsen emphasize that the abscesses in these cases could not have arisen by direct extension, but are inclined to believe that they arose by retrograde extension along the cerebral venous channels. They point out that otitis media may not be recognized, even at autopsy, unless it is carefully sought and suggest that cerebral abscess of "unknown etiology" may often arise from a focus in the ear.

MACKAY, Chicago.

AGE INCIDENCE IN EPILEPSY. A. J. M. BUTTER, Brit. M. J. **2**:714 (Oct. 10) 1936.

Subsequent to a recent reference in the English press concerning the age incidence of epilepsy, a chart is recorded of 300 patients with epilepsy, almost all idiopathic, examined in the past year at St. David's Hospital for male epileptics. All patients were over 15 years of age; 12.3 per cent were over 30 years of age when epileptic seizures began, and in 27 per cent, or the largest percentage for any five year period between the ages of 15 and 30, the onset occurred between the fifteenth and the twentieth year.

BECK, Buffalo.

THE PROBLEM OF GENERAL AS AGAINST FOCAL SYMPTOMS IN CEREBRAL LESIONS. W. MAYER-GROSS and E. GUTTMANN, J. Ment. Sc. **82**:222 (May) 1936.

Mayer-Gross and Guttmann review the ideas of Goldstein and his followers, who, in the past few years, have been extremely critical of the various theories of localization in the brain. Goldstein maintained that localized damage to the brain produces a general disturbance, if one only takes the trouble to make a careful examination of the patient, although certain symptoms are more prominent than others. Goldstein introduced into the field of clinical neurology the psychiatric method of studying "the patient as a whole" rather than his isolated functions. He pointed out that widening the field of examination reveals disturbances everywhere, even in fields which at first glance have no connection with the main symptoms.

Goldstein insisted that every patient in whom one finds evidence of amnesia, disturbance of attention or of spontaneity, impoverishment of ideas and a certain compulsiveness in response to stimuli, disturbances of consciousness and unusual orderliness or slovenliness with affective anomalies should be examined from the point of view of general disturbance of function. The most important finding in cerebral lesions is the catastrophic reaction, by which Goldstein understood the pathologic way in which patients with damage to the brain respond to difficult situations with which they are not able to cope. This consists in perseveration, fatigability, iteration with haste, gradual slowing down and a marked feeling of anxiety.

Overemphasis on localization in the brain has been brought into disrepute by poor logic. For example, because lesions of the frontal lobe were associated with euphoria, it was thought at one time that the frontal lobe was the seat of emotional life. The authors cite Goldstein at length and disagree with him. They cite a

case of a parietal syndrome in which there was no agraphia but marked construction aphasia and acalculia. In this case it is possible to make fine and precise localization. Although the reversal of sleep rhythm may be the only symptom of epidemic encephalitis, one has no hesitation in localizing the pathologic change in the gray matter of the third ventricle. Similarly, in a depression certain symptoms may be absent; yet the diagnosis is not hard to make from the presence of other symptoms.

Mayer-Gross and Guttmann agree with Hughlings Jackson, who maintained that in the highest regions each center represents a large part of the organism, a still larger part in less degree and the whole organism in some degree. They find the solution of the whole problem in stressing not so much the presence of focal symptoms or of general disturbances as the relationship between the focal symptoms and the general reaction, which gives the true picture of what is wrong with the patient. They suggest the introduction of the psychiatric concept of syndromes into the field of clinical neurology.

KASANIN, Chicago.

PROGNOSIS IN CEREBRAL CONCUSSION AND CONTUSION. C. P. SYMONDS, Lancet **1**:854 (April 11) 1936.

Symonds states that the common effects of injury to the head fall naturally into two groups. The outstanding feature of the first group is immediate interruption of consciousness. This may range in degree from a state of automatism to one of stupor, and in duration from minutes to days. The second group includes symptoms such as headache, giddiness, mental change and insomnia. They may occur after consciousness has been regained or without any initial disturbance of consciousness; they may follow the injury at once or after a latent interval of hours or days. Though they show a tendency to improvement and eventual recovery, symptoms of this kind sometimes may persist indefinitely. These two groups of symptoms together present the common sequelae of injury to the head and run their course independently of such complicating features as fracture of the skull and epidural, subdural or subarachnoid hemorrhage. Symonds finds that in the majority of cases in which the outcome is fatal death occurs within the first twenty-four hours but that during the succeeding twenty-four hours the risk is still considerable. Postmortem examination reveals extensive contusion and laceration of the brain. In the group of the most severely injured, a patient who is going to recover will, as a rule, show definite improvement within the first twenty-four hours. After the first forty-eight hours, death from cerebral contusion is uncommon, and the small mortality rate which persists is due mainly to such complications as pneumonia and meningitis. The patient who survives frequently passes through a phase of stupor and delirium, lasting several days, before he becomes mentally clear. On the whole, the longer the duration of traumatic stupor, the greater is the likelihood of troublesome after-symptoms. With the return of consciousness the patient may exhibit changes in disposition or memory. Impairment of intellectual function is, on the whole, commoner and more persistent in patients past middle age. Children, on the other hand, are more likely to exhibit striking changes in character and disposition. Even if at first there is freedom from symptoms, it is not safe to predict an uneventful recovery. In answer to the questions: "Has there been lasting damage to the brain?" and "How long will it be before he gets well?" Symonds makes the following answers: "'We cannot tell until we have seen how much the brain will stand without complaint.' We may safely add that complete recovery is the rule even though the symptoms at first may be severe and improvement slow."

"Neurasthenic" symptoms — anxiety, depression, preoccupation with self, increased liability to mental and bodily fatigue and head discomforts of the functional type—constitute an important part of the aftermath of injuries to the head. They are often precipitated or aggravated by anxiety over compensation. Symptoms of this kind are not likely to be observed in tough-minded persons.

Symonds illustrates mild injury to the head with the case of a man who suffers a blow on the head at football, continues with the game in a state of traumatic

automatism and is later shown to have had a half-hour gap in memory. In nine cases out of ten there are probably no after-symptoms more serious than a headache which is gone on the next day. In the tenth case persistent, and even disabling, liability to headache may supervene, perhaps associated with giddiness, insomnia and fatigue.

As to the ultimate prognosis: The severity and duration of symptoms are directly related to the duration of unconsciousness. Of the common symptoms, giddiness is usually the earliest to disappear. Defective memory and changes in disposition are slow to improve, as also are symptoms of the neurasthenic group. Of all the symptoms, the tendency to traumatic headache is the most persistent. The age of the patient is also an important factor. After the age of 45, the process of recovery is slower than in younger persons. The author draws on W. Ritchie Russell's paper on this subject (*Edinburgh M. J.* **41**:129, 1934) as a source of information. Of a series of 200 patients admitted to the hospital with loss of consciousness, 40 per cent were free from symptoms at the end of two months. Of the 120 patients whose symptoms persisted longer than two months, 66 per cent still had symptoms at the end of eighteen months. The duration of disability depends on several factors. Headache, which is the most persistent of the common symptoms, is likely to remain a source of disability to the manual worker after other symptoms have disappeared. Anxiety over unsettled compensation, or a sense of injustice after settlement, is an important cause of prolonged disability. In Russell's series, in 30 per cent of the cases in which compensation was involved, the patients reported as unfit for full work eighteen months after the accident, whereas the figure for the cases in which there was no compensation was only 9 per cent. In the noncompensation group, 83 per cent of the patients had returned to full work within six months of the accident. In this group 45 per cent of the patients who were over 50 years of age remained unfit for full work at the end of eighteen months. In persons under the age of 40, if no compensation question is present and the injury is one which does not involve loss of consciousness for more than a few minutes, disability lasting more than a few days is uncommon. After a period of unconsciousness up to one hour, nineteen of twenty persons will be back at full work within two months. If stupor persists longer than twenty-four hours the chances are against the patient being fit for work within two months, but eight of ten patients will be able to return to full work within six months of the injury.

WATTS, Washington, D. C.

PROGNOSIS IN MIGRAINE. MACDONALD CRITCHLEY, Lancet **2**:35 (July 4) 1936.

Critchley states that in its severest forms migraine may constitute a distressing and remitting malady which handicaps the victim throughout life. Fortunately, most cases of migraine are mild or so responsive to treatment as to occasion little real disability. It is the author's opinion that migraine starting early in childhood usually reacts to treatment less well than that with onset at adolescence. Female patients respond to treatment about as well as males. Jewish patients respond less well than the average. Patients whose profession entails responsible and exacting brain work, particularly when carried out under sedentary conditions and at high pressure, find themselves at great disadvantage. The cases of severest migraine are often those in which there are multiple precipitating factors. A number of intercurrent affections appear to have a favorable influence on migraine, among which are pregnancy, advancing age, loss of sight and cranial decompression. Patients with headache only, even though severe, respond well to medication. Critchley isolates certain clinical groups in which treatment seems to afford little or no material benefit. Some patients will not persevere with a consistent line of treatment. In cases of intolerance to phenobarbital, addiction to morphine, hypotension, debility and asthenia the prognosis is unfavorable. In cases of migraine closely associated with tangible and inescapable psychologic factors, medicinal treatment is obviously of scant value.

Disabling and debilitating as it is, Critchley finds that migraine is only seldom directly responsible for a fatal event. Chief among the serious complications is

cerebrovascular degeneration. Thus, paralyses of the third nerve (ophthalmoplegic migraine), the oculosympathetic nerve and the face (facioplegic migraine) may occur and persist. Thrombosis of a retinal vessel may occur in the course of an attack and cause a lasting defect in the visual field. Much graver is the development of permanent hemiplegia or aphasia. WATTS, Washington, D. C.

EPILEPTIC CRISES DUE TO MONOBROMATED CAMPHOR. P. PAGNIEZ, A. PLICHET and A. VARAY, Presse méd. **45**:585 (April 17) 1935.

Pagniez and his associates warn against the indiscriminate use of monobromated camphor and point out its epileptogenic properties. They cite three cases in which monobromated camphor was given orally for ailments other than epilepsy and in which epilepsy was never before observed. The observations are typical, with biting the tongue and tonic and clonic convulsions, foaming at the mouth, stertor and semicoma. When injected in the form of an oily solution into the peritoneum or the cerebrospinal cavity, monobromated camphor shows only feeble toxicity, but when given intravenously or in alcoholic solutions, it may easily elicit convulsions. Muskens made similar experiments on cats and found that a dose of 0.5 Gm. increases the animal's tactile and acoustic irritability. With a higher or repeated dose it is possible to obtain a complete epileptic crisis or a fatal issue. It is likely that some persons are intolerant to monobromated camphor, and therefore it is advisable to test the susceptibility of the patient with weak and fractionated doses before administering therapeutic doses. EDITOR'S ABSTRACT.

CEREBRAL DISTURBANCES CAUSED BY VIBRATION OF THE ELECTRIC TREPHINE. E. D. ANDÍA and M. RIVEROS, Fac. de cien. méd. **1**:11, 1936.

Andía and Riveros believe that the noise and terrific vibration caused by the use of the electric trephine are the cause of numerous immediate and remote postoperative sequelae, which they include under the syndrome of *conmoción cerebral.* They believe that the effects are more marked if a large cranial defect is not left, as is the case after simple trepanation. As possible consequences they list: molecular alteration of the cells and arterial reflexes causing anemia, hypertension (presumably intracranial), edema and damage to the fibers connecting the white with the gray matter. NORCROSS, Philadelphia.

CLINICAL, HEREDOBIOLOGIC, AND SOCIAL CONSIDERATION OF HUNTINGTON'S CHOREA. CARLOS LAMBRUSCHINI, Rev. argent. de neurol. y psiquiat. **2**:78 (April-June) 1936.

Lambruschini describes three cases of Huntington's chorea, in one of which there were epileptic attacks. He discusses the relation between epilepsy and Huntington's chorea. Epilepsy in association with Huntington's chorea has been interpreted as an equivalent of chorea. Especial reference is made to the hereditary peculiarities of the disease. Many authors have established the mendelian dominance of the condition. Males are slightly more susceptible than females. Almost 90 per cent of cases occur between the ages of 30 and 45. In some generations in which there are no motor disturbances mental changes occur. In a certain group no direct hereditary influence can be shown. From the sociologic point of view, prophylaxis of the condition involves no marriage or sterilization of the persons afflicted. ALPERS, Philadelphia.

MIGRAINE IN CHILDREN AND YOUTHS. R. HECKER, Monatschr. f. Psychiat. u. Neurol. **94**:173 (Nov.); 237 (Dec.) 1936.

According to Hecker, migraine is commoner during the early years of life than has generally been supposed. He observed fifty-six cases of this disorder in children or youths. The observations were made in a clinic which excluded children below the age of 6 years. Most of the patients with migraine were from 9 to

12 years of age when admitted to the clinic. In the majority of instances the illness began between the ages of 6 and 10 years. In one case the first attack occurred at the age of 1½ years, and in five cases, between the ages of 2 and 3 years. Boys outnumbered girls by approximately 2:1. The fact that 50 per cent of the mothers had migraine points to an important hereditary factor. Endogenous psychoses were not noted among the parents. In two cases a paternal uncle was suffering from epilepsy. Many patients had had several of the infectious diseases common to childhood. As a group, the patients were well endowed intellectually; they were affectionate, lively and frequently sensitive. Gastro-intestinal symptoms, such as vomiting and abdominal pain, were common during the attacks, which were occasionally accompanied by a considerable rise in temperature. The headaches were often followed by prolonged sleep. Epistaxis was not uncommon; in some cases it probably represented the equivalent of a migrainous attack. Transitory visual symptoms were frequently observed. One patient had ophthalmoplegic migraine. Two patients complained of transient sensory disturbances. A distinct psychosis was noted in only one case. The chief symptoms were severe anxiety, excitement and confusion, which lasted for several days. This psychosis was associated with an attack of migraine in a boy aged 13, whose periodic headaches began at the age of 6. In the whole group disturbances in mood were among the most frequent and prominent features of the clinical picture. They were characterized by irritable, peevish and sullen conduct, or less often by seclusive, anxious and tearful behavior. Disturbances in mood were observed before, during and after the paroxysmal headaches, but they also occurred as migrainous equivalents. In a considerable number of instances it was these reactions, rather than headaches, that caused the patients to be brought to the clinic.

ROTHSCHILD, Foxborough, Mass.

CONVULSIVE ATTACKS ASSOCIATED WITH TUMORS OF THE BRAIN. M. N. NEIDING, Opukh. zentraln. nervn. sist., 1936, p. 10.

Neiding reports on the frequency of occurrence of convulsive attacks in seventy-nine cases of tumor of the brain. The diagnosis was verified by operation or autopsy. Convulsive attacks are rare in association with cerebellar tumor. They usually take place in advanced stages of the neoplasm and before death. Neiding believes that such attacks are the result of increased irritability of the cortex induced by partial destruction of the cerebellum. Tumor of the cerebellopontile angle rarely causes convulsions. Such seizures usually indicate expansion of the tumor into the pons, especially during the early stages. In cases of pontile tumor Neiding observed most frequently localized clonic convulsions, and only rarely tonic convulsions of the extremities. As a rule, general fits do not occur in association with pontile growths. They usually involve isolated muscle groups supplied by the cranial nerves. Primary tumor of the pituitary rarely gives rise to convulsive seizures; attacks occur more frequently in cases of suprasellar neoplasm, especially during the early phases. In cases of cerebral neoplasm the type of convulsion depends on the localization of the tumor. Jacksonian fits were seen in cases of deep-seated neoplasms in the basal ganglia, as well as in the motor cortex. In discussing the mechanism of convulsive attacks in association with extracerebral tumor, the author expresses the belief that, in addition to the hydrodynamic changes, the flow of irritation from various parts of the brain to the cortex must be taken into consideration and that one must keep in mind also the increasing excitability of the cortex, caused probably by destruction of certain parts of the brain.

NOTKIN, Poughkeepsie, N. Y.

CLINICAL MANIFESTATIONS OF TUMOR OF THE FRONTAL LOBE. D. A. SHAMBOOROV, Opukh. zentraln. nervn. sist., 1936, p. 63.

Shamboorov analyzes the clinical manifestations in twenty cases of tumor of the frontal lobe verified at operation or autopsy. He comes to the conclusion that there is no special syndrome characteristic of tumors in this location. He adds, however, that there is a relative frequency of certain symptoms. The most fre-

quent manifestations are psychic disturbances, which can be divided into three groups: 1. Psychic retardation bordering on apathy and sometimes complete indifference to the person and to the environment. With this there may be depressive changes in mood. In the early phases there is loss of activity and initiative, while in the terminal stage stupor is usual. 2. Increased psychomotor activity, sometimes reaching the degree of a manic state with confusion. As a rule there is a great deal of irritability. In the terminal stage there is confusion, with increased motor restlessness and sometimes stupor. 3. Changes in intellect and behavior, possibly with additional symptoms characteristic of the two preceding types. The author adds that these types are not always clearcut and are not pure. Among neurologic symptoms he enumerates motor aphasia, jacksonian fits, facial weakness and hemiparesis. Less frequently he found static disorders, a grasp reflex or disturbances in the sense of smell. The last symptoms he singles out as being of particular diagnostic value. The spinal fluid, except for a slight increase in albumin in some cases, is normal. The cerebrospinal fluid pressure was moderately increased in all cases. Periodic headache with transitory psychic disturbances is often the initial symptom. Sometimes the first symptom is a jacksonian fit, motor aphasia or hemiparesis.

NOTKIN, Poughkeepsie, N. Y.

Diseases of the Spinal Cord

SYPHILITIC AMYOTROPHIC LATERAL SCLEROSIS. JUDD SCHULTZ, Bull. Los Angeles Neurol. Soc. **1**:51 (June) 1936.

A man aged 34 had suffered for two years from acute attacks of abdominal pain and vomiting. Serologic tests had given positive reactions for syphilis, but treatment with neoarsphenamine, bismuth and tryparsamide had not produced relief. Six months before examination he lost the sight of the left eye; numbness appeared in the ulnar border of the left arm, and later atrophy began in the small muscles of first the left and then the right hand. Neurologic examination revealed blindness in the left eye with dilatation and fixity of the pupil, though the right pupil reacted both directly and consensually. The muscles of the hands and forearms were atrophic; the left ulnar area was analgesic, and the tendon reflexes were exaggerated in both arms and markedly reduced in the legs. Vibration and position sense were normal. The Wassermann reactions of both the blood and the spinal fluid were positive. The diagnosis was syphilitic amyotrophic lateral sclerosis.

MACKAY, Chicago.

PARAKINETIC MOVEMENTS IN TABES DORSALIS. A. SZÉKY, Monatschr. f. Psychiat. u. Neurol. **93**:292 (July) 1936.

Széky observed a patient with tabes dorsalis who, in the course of the illness, showed pseudo-athetoid movements of the fingers of the left hand. There were impairment of deep sensibility in the left hand and disturbances of superficial sensibility, which extended from the fifth cervical to the first dorsal segments. There was also weakness of the muscles of the shoulder girdle and upper extremity on the left, with slight atrophy, which was most pronounced in the small muscles of the left hand. The pseudo-athetoid movements had apparently developed only after the muscular atrophy had occurred. Therefore Széky believes that a factor in their origin is involvement of the motor cells of the anterior horn.

ROTHSCHILD, Foxborough, Mass.

Peripheral and Cranial Nerves

POLIOMYELITIS VIRUS AND THE DEGENERATION OF PERIPHERAL NERVES. J. A. TOOMEY and H. M. WEAVER, Am. J. Dis. Child. **53**:79 (Jan.) 1937.

The authors compare the effect on the peripheral nerves of animals of poliomyelitis virus given by the gastro-intestinal route (subserosal injection, and that

of the virus administered by intracerebral injection. Sections were studied from the solar plexus and the lateral femoral cutaneous, sciatic and median nerves. Sections from the solar plexus were discarded because they gave no definite information. There was much more consistent and extensive destruction of the axons and myelin sheaths of the nerves of animals receiving virus by the gastro-intestinal route than in those receiving it by intracerebral injection. It is presumed that there is a peculiarity in the nerve pathways from the subserosa of the intestine to the central nervous system, possibly in the nature of conditioning of the nerves to enteric toxins, which accelerates the destructive effects of the virus. Involvement of nerve fibers in animals receiving gastro-intestinal injections probably occurs from the beginning of the disease and is present before there is any marked destruction of the anterior horn cells. It is concluded that poliomyelitis virus may act directly on somatic nerves when introduced via the gastro-intestinal tract.

WAGGONER, Ann Arbor, Mich.

LOCALIZED RADICULITIS AND NEURITIS. JOSEPH C. YASKIN and CLARENCE A. PATTEN, Am. J. M. Sc. **192**:650 (Nov.) 1936.

Localized radiculitis may be caused by lesions of the sensory or motor roots in the subarachnoid space, the osseous intervertebral canals and in their distal course to form plexuses or peripheral nerves. The symptoms are segmental (radicular). The most conspicuous symptoms are sensory, with pain a constant feature. With involvement of the motor roots, weakness, atrophy and changes in electrical reactions occur. In general, the etiologic diagnosis of radiculitis requires investigation for syphilis, tuberculosis or neoplastic disease. Among the conditions to be considered are tumor of the spinal cord, myeloradiculitis or myeloradiculoneuritis, osseous disease about the vertebral column, pelvic tumor and focal infection. Treatment is most satisfactory in elimination of the underlying cause.

The causes of localized neuritis vary from direct trauma to focal infection. The symptoms consist generally of sensory, motor, trophic, vegetative, reflex and electrical manifestations. Pain follows the distribution of the affected nerve, which is tender on pressure. All forms of sensory disturbances may be demonstrated objectively within the cutaneous distribution of the affected nerves. Motor disturbances vary from mild weakness to complete paralysis. Trophic and vasomotor changes are reflected in the skin and its appendages. The diagnosis of neuritis should be made only after the exclusion of (1) local disease of the muscle, bone, joint or blood vessels (2) radiculitis, (3) disease of the spinal cord or brain and (4) neuralgia.

MICHAELS, Boston.

HERPES ZOSTER WITH PARALYSIS OF ONE SIDE OF THE FACE. ARTHUR G. SCHOCH, Arch. Dermat. & Syph. **34**:686 (Oct.) 1936.

In a case of herpes zoster reported by Schoch, typical cutaneous lesions were found on the right side of the neck, the lobe of the ear and the mastoid region. However, the unusual feature in the case was the presence of complete paralysis of the right side of the face, of the peripheral type, which appeared with onset of the herpes. Treatment consisted of the injection of 1 cc. of solution of posterior pituitary U. S. P. This dose was administered on the first, second and fourth days after the appearance of the palsy. Within two weeks, both the cutaneous lesion and the paralysis had disappeared.

DAVIDSON, Newark, N. J.

PRIMARY TUMOURS OF THE ROOT OF THE FIFTH CRANIAL NERVE: THEIR DISTINCTION FROM TUMOURS OF THE GASSERIAN GANGLION. HUGO KRAYENBÜHL, Brain **59**:337, 1936.

Two cases of tumor arising from the root of the fifth nerve are reported by Krayenbühl, and an analysis is made of the difference in the clinical picture of

tumor of the ganglion and that of tumor of the nerve behind the ganglion. The first case was that of a man with a three years' history of symptoms that pointed to a lesion of the left cerebellopontile angle. Neurologically, he exhibited bilateral anosmia, bilateral papilledema and lateral and upward nystagmus. There were: absence of both corneal reflexes; anesthesia and analgesia of the left side of the face complete over the ophthalmic division and partial over the maxillary and mandibular divisions; normal power in the masticatory muscles; severe weakness of the upper and lower parts of the face on the left; deafness in the left ear; hypotonia of all the limbs, and slight weakness of the right upper limb. There were absence of all the abdominal reflexes and an extensor plantar response on the left side. Autopsy revealed a neurofibroma of the trigeminal nerve, situated largely in the left cerebellopontile angle. The seventh and eighth nerves were not connected with the tumor; in their proximal part the fibers of the fifth nerve spread out in the capsule, and in their distal part they were lost in the substance of the tumor. The rostral portion of the tumor occupied Meckel's cavity, but there was no evidence that the tumor arose in the gasserian ganglion.

The second case was that of a man with an illness of six years characterized by headache, sensory disturbances in the right side of the face, staggering, deafness and mental deterioration. From the onset of the illness he had a feeling of numbness on the right side of the face and at times some pain. On examination there were slight deviation of the jaw to the right and bilateral diminution in the sense of smell. On the right side there were external squint and amblyopia, absence of the corneal reflex, slight relative anesthesia to cotton wool over the side of the face and relative analgesia in the distribution of the ophthalmic division. There were weakness of the lower left side of the face, incomplete deafness bilaterally and mild hemiparesis on the left, with increased tendon jerks and an extensor plantar response on the same side. At necropsy a neurofibroma was observed in the right cerebellopontile angle, extending forward into Meckel's cavity and beneath the floor of the third ventricle.

Analysis of reported cases of tumor of the gasserian ganglion and of the trigeminal root discloses the probability that pain occurs when the ganglion is primarily involved and is usually absent when the tumor begins on the trigeminal root. Of the two cases reported by the author, pain was absent in the first and of minor importance in the second. Tumors of the trigeminal root present a variety of initial symptoms. The symptomatology is indicative of cerebellopontile involvement. In only two cases was the illness initiated by sudden facial numbness. During the further course of the illness, trigeminal symptoms become more conspicuous, a feeling of numbness, coldness and tingling in the face being prominent. Pain was constant and severe in only two cases. Objective sensory loss was marked in the whole series.

The main diagnostic difficulty is in distinguishing between a tumor of the trigeminal root and one of the acoustic nerve. In cases of tumor of the acoustic nerve the degree of deafness and vestibular loss is usually greater than that of trigeminal sensory loss on the side of the lesion but this is not invariably the case. In cases of tumor of the trigeminal root, however, the degree of objective sensory loss is not always greater than that of deafness. Thus, there are many cases in which a precise differential diagnosis cannot be made. In certain cases forward extension of a tumor of the trigeminal root at a relatively early stage will give distinctive signs. The early sensory and motor involvement of the trigeminal nerve, coupled with evidence of pressure on the adjacent cerebral peduncle, presents a clinical picture from which the correct diagnosis can be made. A further aid in diagnosis is afforded by the fact that these tumors, because of their almost invariable extension into the middle fossae, often produce ocular palsies.

SALL, Philadelphia.

HYPERALGESIC MOTOR REACTIONS. T. ALAJOUANINE and R. THUREL, Encéphale **31**:169, 1936.

Hyperalgesic reflexes, first described by Babinski and Jarkowski in 1921, are motor responses to painful stimulation of a hyperalgesic cutaneous area. Slight stimulation of such a zone may be painful. The painful quality is present even when the hyperalgesic area is anesthetic and the patient does not perceive the nature or situation of the stimulus. Hyperalgesic reactions may occur during unconsciousness, as in coma. The motor response is generally retraction of the extremities, which is part of the panic response called forth by the peculiar painful quality. In the lower extremities the movement is immediate and sudden and consists of a triple flexion with medial rotation of the feet and flexion of the toes. It occurs only in regions where the pyramidal innervation is intact and differs from spinal automatism. Thus, in the Brown-Séquard syndrome the hyperalgesic, paralyzed extremity when stimulated responds with a movement of spinal automatism, consisting of slow flexion with extension of the toes. The nonparalyzed extremity responds with a typical hyperalgesic motor response to stimulation of the hyperalgesic paralyzed extremity. Local ischemia of the leg, produced by an Esmarch bandage, prevents spinal automatism but does not interfere with the hyperalgesic reaction. The hyperalgesic reaction is not adapted to the site of the cutaneous stimulus, which is often poorly localized. It is different in this respect from voluntary movements, the purpose of which is to withdraw the part of the body receiving noxious stimulation. In like manner it differs from the true defense reflexes of Guillain and Barré which reproduce in unconscious patients the defense phenomena observed in decapitated frogs. The phenomena of repercussivity of André Thomas differ from hyperalgesic reactions in that the former take place only in the territory corresponding to the injured nerve centers; they can be called forth not only by peripheral stimulation but by emotions. Their painful quality is due to the kind of stimulus and not exclusively to the site of stimulation, as in hyperalgesic reflexes. For the same reasons, spasmodic synkinesias, which can be compared to phenomena of motor repercussivity, differ from hyperalgesic reactions. Hyperalgesia must be attributed to disturbance of the sympathetic innervation, which explains the fact that its territory may be greater than that of the cerebrospinal lesion and the apparently paradoxical coexistence of anesthesia and hyperalgesia.

LIBER, New York.

Congenital Anomalies

OXYCEPHALUS: PREMATURE SYNOSTOSIS OF THE CRANIAL SUTURES. A. E. BENNETT, J. J. KEEGAN and H. B. HUNT, J. Nerv. & Ment. Dis. **84**:274 (Sept.) 1936.

Little information is available in the literature on the surgical treatment of oxycephalus. Von Graefe and MacKenzie were the first to call attention to the premature closure of the coronal and sagittal sutures, causing anteroposterior shortening of the skull and the so-called tower, or steeple, skull. The specific etiology is unknown. The disease is congenital but rarely familial and is associated with other congenital defects, such as syndactyly and hemolytic icterus.

The authors report two cases in which examination was made before there had been permanent damage to the optic nerves from intracranial pressure. Successful surgical results were obtained in the first case, that of a boy of 4 years, by a combination of temporal decompression and crucial craniectomy, and in the second case that of a girl 3½ years, by circular craniectomy after the method of Bauer. While operation was performed late in these cases, mental improvement and saving of vision resulted in both. The authors believe that intervention is preferable in the first year of life, when the cranial bones are thinner and more pliable and before intracranial pressure has produced atrophy of the optic nerve.

HART, New York.

Diseases of Skull and Vertebrae

A New Classification of the Bones Forming the Skull, with Surgical Applications, Especially as to the Relation of Osseous Infections to Meningitis. Wells P. Eagleton, Arch. Otolaryng. **24**:158 (Aug.) 1936.

Eagleton presents an account of his progressive studies on infections of the petrous apex. His initial successes were followed by several failures, which led him to further study to determine why in certain cases infection of the petrous apex causes a recrudescence of meningitis. To determine this, he studied the bones of the skull from a functional as well as from a morphologic standpoint. He stresses the embryologic development and growth of the bone and the reaction of different bones to infection. The special sense organs, having developed from the lowest types of sea life to the present forms found in man, are really extensions of the brain, protected each in its peculiar manner to conserve the purpose intended for it. Therefore, the bones of the skull should be considered not only from the standpoint of their protection of special sense mechanisms and nerve tissue but for their regional position and variation in protective mechanisms against violence and infection, depending on the origin, position and function of the bone involved. The bones of the skull grow not only from mesodermal tissue but from the ectoderm, the tissue from which pure nerve tissue is formed. Therefore, to grasp the significance of a bone of the skull, one should make use of four factors: (*a*) embryologic origin, (*b*) functional use, (*c*) stage of growth and (*d*) position in relation to the contained organs and surrounding structures.

In general, there are two kinds of somatic bone: compact bone tissue and cartilage bone. The bone grows by two distinct processes, deposit of calcium salts and vascular penetration. In somatic bones there are deposition and, later, absorption of tissue, with differentiated division according to the function of the bone. The growth processes occur in the center and at the periphery. Each bone during its period of growth passes through youth, maturity and old age. The stage of development in which the bone is at the time of infection accounts for the different reactions. The bone of the labyrinth is senescent at birth, whereas the base of the sphenoid bone never grows old. The bones of the cranial vault evolve from membrane; compact special sense bones spring from cartilage; protective, pneumatic bone develops from a combination of the two, and actively protective bones contain red bone marrow, which gives them, in addition to their function of protection by position, that of special protection against infection and the ability to participate in the hemocytopoietic system. The pneumatic bones grow from cartilage but have a covering of membrane bone. Their function is to protect a special sense organ against violence and infection. Pneumatization is infiltration of the bone with ectodermal tissue, a part of the reticulo-endothelial system. The petrous apex as a source of meningitis has frequently been overlooked, even at postmortem examination, because the red marrow within it does not react to infection by the production of visible necrosis until weeks have passed. Infection in this region is often by blood vessels entering the meninges, resulting in meningitis long before the infection of the bone marrow is discernible to the naked eye. Acellular fat marrow can become cellular red bone marrow in response to a stimulus. Each kind of bone in the temporal bone is in a different stage of growth, the labyrinth being senescent at birth, the membrane bones continuing to grow until the fontanels have closed and the end of the petrous tip containing red bone marrow throughout life. The mastoid apophysis increases in size by osseous palingenesis; this development of mammalian pneumatic bone is a type of passively protective surface, special sense meso-ectodermal archegenesis, a specialized modification which was evolved by avian life. Passively protective pneumatic bones grow during infancy and early childhood. Surgically, the base of the sphenoid

bone should be regarded not simply as a mechanically protecting bone but as a constantly working histogenetic organ for metabolic activity, possessing specific bactericidal properties. It is an adaptation of the bodies of the vertebra.

HUNTER, Philadelphia.

CLINICAL FORMS OF OSTEOMYELITIS OF THE ROOF OF THE ORBIT. G. WEILL and A. KOUTSEFF, Rev. d'oto-neuro-opht. **14**:629 (Nov.) 1936.

Two cases are reported, both of osteomyelitis of the lesser wing of the sphenoid bone and both of fatal outcome due to meningitis. Osteomyelitis of the lesser wing of the sphenoid bone is so rare that in 1921 Cange discovered only one indisputable case in the literature. Clinically the condition is characterized by acute palpebral edema (not under marked tension), unilateral exophthalmos, integrity of the neighboring accessory sinuses, normal results on puncture of the orbit and early acute aseptic meningitis, complicated with papillary stasis, paralyses of the oculomotor nerve and cerebral abscess. Taken together, these symptoms aid in differentiating the condition from acute inflammatory disease of the orbit, sinusitis or suppurative phlebitis of the cavernous sinus.

DENNIS, San Diego, Calif.

Society Transactions

CLEVELAND NEUROLOGICAL SOCIETY

ALEXANDER BUNTS, M.D., *Chairman*

Regular Meeting, Jan. 20, 1937

SYMPOSIUM ON THE CHOREAS

CHOREA WITH HEMIBALLISMUS AS A SYMPTOM OF HYPERTENSIVE ENCEPHALOPATHY: REPORT OF A CASE. DR. ROGER F. SCHERB.

A white woman aged 57 was admitted to the psychopathic division of the Cleveland City Hospital on Oct. 19, 1936, with the complaint of violent jerking of the right arm and leg, nonsensical talk and unprovoked crying spells, of two weeks' duration. She had been hospitalized in June 1935 for four weeks, the diagnosis at the time being toxic psychosis with hypertensive cardiovascular disease. Two attacks of right hemiplegia with aphasia had occurred seven years and one year prior to the first admission, respectively, the second stroke leaving slight weakness of the right upper and lower extremities and a mental change designated as increased irritability and nervousness. Two weeks prior to the present admission violent thrashing movements of the right leg and arm began gradually, without loss of consciousness. These increased in severity, giving the patient no rest. Because of the associated dysphoria and irrelevant speech, she was admitted to the hospital.

On admission the patient was in constant turmoil due to irregular, uncontrollable movements, of large amplitude, involving the right extremities. The arm frequently described an arc, going through somewhat of a ball-throwing movement. The head was frequently pulled toward the right shoulder, and slight grimaces appeared on the right side. The movements ceased if the patient abstained from trying to initiate any activity. She could understand what was said to her and named objects correctly, but in speaking she frequently used words irrelevant to the stream of speech; she realized this and tried to correct herself. Her mood was dysphoric. Physical examination revealed hyperactivity of the tendon reflexes but no clonus. No pathologic reflexes were elicited. The blood pressure was 235 systolic and 125 diastolic; the heart was enlarged to the left anterior axillary line. The eyegrounds showed marked evidence of hypertensive vascular disease.

It was decided to administer pyretotherapy, and chills were induced on ten occasions by intravenous injection of typhoid vaccine. The hemiballismus gradually subsided, even before the typhoid vaccine was given, none being observed after the sixth hospital week, although choreiform movements of small amplitude still persist on the right side. During the course in the hospital the patient has had two acute cerebral accidents, manifested mainly by sensory aphasia, which rapidly disappeared. The last attack left increased spasticity of the right lower extremity, with hyperactivity of the knee and ankle jerks and ankle clonus but no Babinski sign. The first cerebral accident occurred while the hemiballismus was decreasing and seemed to accelerate its subsidence.

This case is interesting not only because hemiballismus is unusual but because it subsided. Martin and Alcock (*Brain* **57**:504, 1934), in a search of the literature, found 14 cases, in addition to 2 of their own, in which the only lesion observed postmortem was a small one involving the contralateral corpus Luysi. They expressed the opinion that damage to this structure results in hemiballismus, while it is not disproved that damage to other structures may also cause it. In a case cited by them the only demonstrable lesion was in the putamen. Lhermitte and

Wenderowič (*Ztschr. f. d. ges. Neurol. u. Psychiat.* **114**:78, 1928) maintain that lesions situated elsewhere, such as in the cerebellocerebral and dentatorubral tracts, may give rise to hemiballismus. This is in line with Wilson's hypothesis that athetosis and chorea are due to "afferent derangement" of the cerebellomesencephalothalamocortical system, exteriorized through the corticospinal system, and that no single, invariable anatomic lesion is to be found. In my case it is probable that there are multiple vascular lesions. Subsidence of the hemiballismus may have been due to the corpus Luysi having been rendered functionless only for a time as a result of a neighboring lesion, as was suggested in a case referred to by Martin and Alcock.

CHOREIFORM MOVEMENTS ASSOCIATED WITH PRESENILE DEMENTIA: REPORT OF A CASE. DR. ROGER F. SCHERB.

A woman aged 60 was admitted to the psychopathic division of the Cleveland City Hospital in October 1935, because of gradual loss of memory, confusion and disorientation. For two years before there had been gradual mental deterioration in the form of loss of memory, failure to recognize members of her family, incoherent speech and, finally, inability to care for herself. For eight months prior to admission she had what were designated as fainting spells, during which she became rigid and on one occasion bit her tongue.

On admission physical examination gave normal findings. Neurologic examination showed generalized hyperreflexia, absence of abdominal reflexes and a Babinski sign on the left. Ophthalmoscopic examination revealed narrowing of the arteries, but otherwise nothing abnormal. Examination of the spinal fluid on three occasions showed normal appearance and pressure and a negative reaction to the gum mastic test; the cell count varied from 3 to 12 lymphocytes per cubic millimeter, and the Pandy reaction from negative to 3 plus. The Wassermann reactions of the blood and spinal fluid were negative. An encephalogram showed internal hydrocephalus, marked diffuse cortical atrophy and questionable porencephaly on the left.

Since admission the patient has been severely demented. She rarely utters an intelligible word; mumbling and guttural sounds alone are heard. Occasionally she seems to recognize her relatives. She must be cared for in every detail. There are no recognizable emotional responses except an occasional cry if she is moved from her chair. Sporadically throughout the day quick, jerky choreiform movements of the upper extremities, head and face are manifested. The lower extremities often show adductor spasm with scissors posture. There is generalized hypertonicity. Up to the present there have been sixteen epileptiform convulsions.

Since there is no evidence of diffuse vascular disease and no history of acute vascular episodes, but instead gradually progressive dementia to the level of idiocy, accompanied by epileptiform seizures, my colleagues and I think that the condition is presenile dementia—probably Pick's or Alzheimer's disease. The patient is too young for true senile dementia. However, as is usual in cases of these two encephalopathies, a final opinion can be given only at necropsy.

DISCUSSION

DR. LOUIS PILLERSDORF: That severe loss of brain tissue has occurred in the second case is substantiated by the air studies. Whether the disturbance falls into the category of presenile dementia, either Alzheimer's or Pick's disease, is difficult to say from clinical evidence.

A CASE OF HUNTINGTON'S CHOREA. DR. CHARLES L. LANGSAM, New York.

A white man aged 52, who was admitted to the City Hospital on Sept. 3, 1936, had previously been intelligent, having graduated from an engineering school some time before the World War. He held a responsible position as an engineer in Canada for two years and then enlisted in the army as an ambulance driver in

1914. After the war he again worked for a railroad company until 1932, apparently filling a fairly responsible position as civil engineer, although his foster-father said that he had shown gradually progressive mental deterioration since about 1919. In 1932 he gave up his job and went to Florida; since then, he has not worked and has been indigent. On the day before admission he appeared in Cleveland with the symptoms of choreiform movements; he was extremely nervous and was immediately hospitalized.

The family history is interesting in that the patient's mother had been an inmate of several sanatoriums, the last being Brigham Hall Hospital, Canandaigua, N. Y., where she was incarcerated from July 9, 1905, until her death on Feb. 12, 1906, from lobar pneumonia, at the age of 61. Her condition was diagnosed as Huntington's chorea.

On admission the patient's behavior on the whole was childlike and regressive, and his general appearance was that of a man older than his stated age. Speech was coherent, but jerky and replete with ideational flight, making it difficult at times to follow his trend of thought. He was euphoric. No trend reactions were elicited. Minor defects were apparent in both recent and remote memory, and retention and recall were impaired. Insight was lacking, and judgment was poor.

During the examination he made continuous, purposeless movements, shrugging his shoulders, bobbing his head from side to side and moving his jaw, toes and feet. The gait was stilted and unnatural—somewhat theatrical and bizarre. Physical examination gave essentially normal results; the blood pressure was 134 systolic and 80 diastolic, the pulse rate 66 and the respiratory rate 20. All cranial nerves were intact. The reflexes were physiologic except for slight exaggeration bilaterally of the suprapatellar and patellar responses and absence of the abdominal and cremasteric reflexes. There was no marked ataxia on purposeful movement, although there was some incoordination of the muscle groups on initiation of movement. Sensory examination gave normal results. Serologic reactions of the blood and spinal fluid were negative, and the protein reaction of the fluid was faintly positive.

Since admission the patient has remained euphoric and childish. Urinary infection developed and subsequently abated. The tremor has persisted, including twitching about the mouth, smacking of the lips, occasional involuntary upward rolling of the eyeballs, shrugging of the shoulders, jerky, bizarre gait and posture and theatrical attitudinizing. At times he has been manneristic and inaccessible; he has expressed numerous somatic delusions and complained of bodily ailments. His mental condition has retrogressed somewhat, becoming gradually more dilapidated, and the involuntary movements have become more pronounced.

The history of gradually developing mental deterioration in both the intellectual and the emotional sphere, the objective neurologic data, most significant of which are the numerous choreiform movements, and the history of a similar neurologic disorder in the patient's mother stamp this case as one of Huntington's chorea.

Spasmodic Torticollis: Report of a Case. Dr. Guy H. Williams Jr.

Spasmodic torticollis has long been recognized as a definite clinical entity. Present day methodology has contributed little to an understanding of spasmodic torticollis, and there is little to add to the accurate observations of Gowers and of Oppenheim.

W. B., a white man aged 50, was admitted to the neuropsychiatric service of the Cleveland City Hospital on Aug. 22, 1936, with the complaint of "turning the head to the left." The illness dated back to October 1935, when the patient first noticed slight nervousness and a gripping sensation in the left side of the neck. At first this distressing symptom harassed him only while working, his occupation being that of a street-car conductor. It is interesting to note that for the past fifteen or twenty years the patient had been stationed to the right of the exit door on the street-car and it was necessary for him at each stop to turn his head sharply to the left so that he might observe the exit of passengers. The

disease progressed, so that in April 1936 he was forced to stop work; he has been idle since. The illness showed no tendency toward abatement, and in June 1936 he had spasmodic twisting of the head to the left, even while reclining. It was only after a long period of absolute rest that he was able to inhibit the movement at all. The patient said further that walking or any other voluntary movement aggravated the twitching and that he was certain that emotional excitement made it worse. Because of the increasing frequency of the spasmodic twitching and the reactive emotional depression that it invoked, he sought medical relief.

His mother is living and well, at the age of 80. However, a maternal aunt became nervous at the age of about 52. The patient was unable to delineate her illness clearly except to state that she was reputed to have "shaken all over."

Examination revealed an asthenic man who continually supported the left side of his face with his left hand; the chin was pointed to the left and was slightly elevated and the right ear tended to approximate the medial end of the right clavicle. There was intermittent twitching of the head and neck, chiefly to the left, and tonic and clonic spasms of the right sternocleidomastoid muscle were observed. The right shoulder was slightly drooped, and the right arm, when hanging at the side, was held slightly back of the normal position, indicative of mild torsion of the trunk. The gait was normal, but the twitchings of the head and neck were accentuated during walking. Synkinesias were neither decreased nor exaggerated, except perhaps for occasional slight grimacing. There was definite hypertrophy of the right sternocleidomastoid muscle. Examination otherwise gave essentially normal results, as did laboratory tests including studies of the blood and spinal fluid.

From the etiologicopathologic standpoint, the many theories promulgated to explain the genesis of spasmodic torticollis, which place its origin in sites anywhere from the cortex to the muscles themselves, are only a hopeless confession of ignorance. Oppenheim ventured the belief that the disease is due to irritation of the nerve centers. His explanation, which agreed with that of Brissaud, was that spasmodic torticollis is a psychomotor disease, or a movement of expression which becomes imperative. In recent years it has been believed that the affliction is a fragment of dystonia and arises somewhere in the extrapyramidal motor system. Foerster spoke of spasmodic torticollis as "the cornerstone of the athetoid motility play."

Oppenheim ascribed cases of spasmodic torticollis to chronic poisoning and infectious diseases, as well as to ocular paralyses and errors of refraction. Other factors, ranging from disease and displacement of cervical vertebrae to disease of the muscles themselves, have been proposed in the genesis of this entity, but none of these contentions has been proved to a convincing degree. Occupational spasmodic torticollis has been described by several observers. It has been thought that excessive use of muscles resulting in exhaustion is a probable etiologic factor. Annandale described it in a woman who was a weaver, and Kinnier Wilson reported a case of torticollis developing in a woman who had been a mail sorter for years. Finally, members of the psychoanalytic school have ascribed this disease to the operation of psychogenic factors. While most workers do not agree with this concept, many believe that there is a neurotic or psychotic element in many cases.

From the standpoint of permanent relief, there is little that offers hope. Both surgical methods and psychotherapy have been used in treatment; good results have been claimed by the exponents of both procedures, but, so far as I can see, surgical intervention probably offers more, at least when the disturbance is of prolonged duration.

In regard to the final crystallization of the diagnosis in the case reported: The differential diagnosis rests between Huntington's chorea and spasmodic torticollis. With the history that a maternal aunt had a nervous disease, one cannot completely exclude Huntington's chorea as a possibility. However, this man's behavior has been that of a so-called normal person during his two months of residence at the hospital, and there is nothing in the objective or subjective data

to indicate mental aberration of any sort. I think that this man's occupation may have played an important part in the production of the clinical syndrome, and for the time being I am content with the diagnosis of spasmodic torticollis.

DISCUSSION

DR. LOUIS PILLERSDORF: I am profoundly impressed by the major influence of the psyche in spasmodic torticollis. The fact that gentle support of the chin can check the powerful torsions produced by the rotatory muscles of the head is significant. The best results which I have seen, however, have been obtained by neurosurgical methods.

DR. W. JAMES GARDNER: I have never seen any one helped in this condition, except by nerve section. From a neurosurgical standpoint, may I call attention to the constancy of the pattern of movement? The operation which gives the most promising results consists of division of the spinal accessory nerve near the muscle and of the anterior roots intradurally.

DR. ROGER E. PINKERTON, Akron, Ohio: Has a long-continued support been used in cases of this sort?

DR. GUY H. WILLIAMS JR.: Concerning the psychic factors conceivably operative in this case, as suggested by Dr. Pillersdorf: I may state that the personality of the patient was well balanced prior to the illness; there was nothing in the development of personality which indicates a major psychic influence. Now, however, he has a tendency to brood and shows an affective response concomitant with that expected in a person whose insight makes him realize that he is suffering from a disabling disease.

In response to Dr. Pinkerton's question: A review of the literature reveals that mechanical supports have been found of little value and, indeed, have been known to do definite harm.

HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE) WITH THE KAYSER-FLEISCHER CORNEAL RING. DR. JUSTIN M. HOPE.

Progressive lenticular degeneration, a comparatively rare clinical entity, described by S. A. Kinnier Wilson (*Lancet* **1**:1115, 1912) and commonly designated as Wilson's disease, is best termed hepatolenticular degeneration, as suggested by Hall in 1921, for this term emphasizes the importance of the hepatic lesion.

M. F., a white woman aged 28, was admitted to the City Hospital on Oct. 10, 1936, with the complaint of shaking of the arms and legs. She dated the onset of illness to the morning of March 6, 1927, when she awakened with what she called a "stroke." The so-called stroke consisted of weakness of the left side of the face, drooping of the left corner of the mouth and inability to close the left eye. Within two weeks the weakness of the face vanished; probably it was mild Bell's palsy, unrelated to the present illness.

The patient was well after this incident until 1929, when she noticed a slight difficulty in speech. One year later she noticed tremor of the right hand, which was at first slight and inconsequential and predominantly of the intention variety but gradually increased in severity and extent, being present at rest as well as on voluntary innervation, and came to involve the left hand and arm as well as the right. In 1931 a diagnosis of Parkinson's disease was made by the family physician. In 1932 there developed tremor of both legs, which was most marked when she seated herself and attempted to extend the lower extremities. There was no subjective weakness or abnormal sensation. The tremor of all four extremities soon became so marked that the patient was practically incapacitated. In 1935, while at a nursing home, she improved sufficiently to walk without aid. She remained improved, being able to dress herself, walk without assistance and do various odd jobs about the home until March 1936, when suddenly, well-nigh overnight, she became much worse, the tremor increasing and being present almost

constantly except while sleeping. There were gradually increasing difficulty in speech and progressively ensuing euphoria, which the patient herself was at times able to appreciate.

In 1918 the patient had had an attack of influenza which, in itself, presented no startling eventualities. The only noteworthy fact obtained in the family history was that there was no similar nervous disease in any other member of the family.

Physical examination revealed that the patient was moderately well nourished; the features were fixed and devoid of expression except for a vacuous smile, which appeared frequently; the mouth was held constantly open, and saliva occasionally drooled from the corners. The patient understood commands and cooperated in the examination; her basic mood, however, was one of euphoria, and she seemed to be as unaware of the spasmodic depression of the inferior maxilla as she was indifferent to the tremor and oblivious to the sialorrhea. There was also evidence of failing memory, as she was unable to recall details of her illness of which she was aware on admission. When the patient was at rest the arms were adducted, the forearms pronated, the elbows and wrists flexed and the fingers extended. The legs were extended and the feet and toes flexed. The tremor, which constituted one of the most constant and distressing features of the illness, was a true tremor. It was markedly increased by excitement and voluntary innervation or when attention was drawn to it. There was marked spasticity of the muscles, most marked in the large joints of the upper extremities. Whatever passive movement was imparted to one group of muscles was resisted to a considerable degree by the opposing muscle group, which rendered quick, passive to and fro movements of the extremities impossible. Contractures were not prominent in this case. There was marked dysarthria of speech, which was characterized by the slurring element without the staccato quality of speech associated with disseminated sclerosis. Dysphagia was not in evidence; muscular weakness was present, most marked in the extensor muscles of the upper and lower extremities. Volitional movements were performed well in range, but they were inhibited with comparative ease. A ring of olive-brown pigment, situated at the limbus—the Kayser-Fleischer ring—merged with the cornea, which was of normal transparence toward the center. Neurologic examination otherwise gave essentially normal results. The cranial nerves were intact; there were no abnormal sensory findings, and the tendon reflexes were active but not exaggerated. The abdominal reflexes were obtained with difficulty because of the spastic condition of the abdominal musculature. Babinski and Hoffmann signs were not elicited. Physical examination made as a routine, including that of the heart, lungs and abdomen, revealed nothing abnormal, and the liver was not palpable.

There was moderate secondary anemia, but otherwise the laboratory findings were essentially normal. The galactose tolerance test for liver function was well within normal limits.

The hospital course has not been remarkable. The patient is holding her own, without marked progression of the disease, as indicated by the clinical manifestations.

According to Walsh, the clinical course of hepatolenticular degeneration, although variable, may in most cases be divided into three phases. The first phase is that of involvement of the liver; fever, vomiting, diarrhea, jaundice, epistaxis and ascites may occur. The liver and spleen are enlarged during this period, but tests for liver function yield normal results. The diagnosis of hepatolenticular degeneration is possible in this early phase only by finding the corneal ring. A presumptive diagnosis is made possible by the presence of a positive family history.

The second phase of the disease is a period of latency during which the patient feels well and the liver and spleen become reduced in size. The diagnosis in this phase is again possible only by finding the corneal ring. The duration of this phase is variable; months, or even years, may elapse before the development of symptoms referable to the central nervous system. The longest duration on record is eleven years.

The third phase is that of involvement of the nervous system. The predominant symptoms are those to be ascribed to degeneration of the lenticular nuclei, although in some cases symptoms referable to degeneration of the frontal lobe and cerebellum have been found. The neurologic signs may be variable in this phase, but the case reported here serves to illustrate the typical clinical syndrome as described in the original work of Wilson, except for the diagnostic Kayser-Fleischer ring, which was present in my case and was not described in Wilson's original work.

The Kayser-Fleischer ring, which is seen in the corneas of the majority of patients with this disease, may be present in all phases of the disease; when present, it is diagnostic. The ring, which is situated at the periphery of the cornea, is usually complete; it is olive brown and about 2 mm. in width. With the slit lamp it is seen to lie in Descemet's membrane and to consist of granules of brown pigment, which are less than 1 micron in diameter.

Kayser in 1902 first described the ring in a patient thought to be suffering from multiple sclerosis. Fleischer in 1903 and Salus in 1908 observed the ring in patients who were also thought to have multiple sclerosis. Fleischer in 1909, and again in 1912, called attention to association of the corneal ring with hepatolenticular degeneration. Hall in 1921, after a study of 9 cases, stated that the pigment was endogenous, to which Fleischer agreed in 1922. After this, a number of spectroscopic examinations of the pigment were made, and the majority of observers agreed that the spectrum is closely related to that of urobilin. Greenfield, in a study of 2 cases, stated that the pigment reacts chemically in a way similar to that of malarial pigment, which is derived from hemoglobin. For this reason, he expressed the belief that the ring pigment was probably also a derivative of hemoglobin. This is the consensus of ophthalmologists at present, although there is no iron in the pigment.

DISCUSSION

DR. LOUIS PILLERSDORF: I am not completely convinced that the case presented is one of Wilson's disease. My reasons are: First, a familial history the importance of which is emphasized by Wilson, is not present in this case; second, the corneal ring has not been subjected to examination with the slit lamp, and third, the patient has a history of influenza during the epidemic of 1918, so that she may be suffering from a chronic encephalitic process affecting not only the nuclei of the basal ganglia but their cerebellar connections.

DR. JOHN D. O'BRIEN, Canton, Ohio: Wilson emphasized that patients with disease of the striatum never cross their legs. As this patient was wheeled into the clinic, I observed that her legs were crossed, in consequence of which there is doubt in my mind as to the diagnosis.

DR. CHARLES DOLEZAL: To my mind, the presence of cirrhosis of the liver has not been clearly demonstrated in this case. Even though the liver is not palpable and the functional tests are normal, it is rare to find a case of cirrhosis in which there is not at least anemia.

DR. JUSTIN M. HOPE: In response to the questions of Dr. Pillersdorf: The attack of influenza from which the patient suffered in 1918 was extremely mild and was characterized only by a slight rise in temperature, general malaise and some cough. The entire illness was over in forty-eight hours, and there were no evidences of hypersomnolence before, during or after the illness. Then, too, the objective neurologic findings are not consistent with the diagnosis of a parkinsonian syndrome associated with chronic encephalitis. The general appearance of the patient, with distortion of the physiognomy in a vacuous grin, depression of the inferior maxilla and drooling of saliva, is identical with that in cases described originally by Wilson. The pictures in the original cases, emphasizing the facial expression and the general bodily configuration, are an exact counterpart of those in this case. The tremor of Parkinson's disease is traditionally a static rhythmic tremor which improves on intention. The tremor in my patient, although a true tremor, is more coarse and irregular and is markedly accentuated on voluntary innervation.

In a search of the literature, I have been unable to find a case of Parkinson's disease in which the Kayser-Fleischer ring has been described. The diagnosis of the corneal ring was confirmed by the ophthalmologist at the hospital, who stated that slit lamp examination is not necessary to recognize this lesion.

Regarding the question of familial history: I may say that of the 12 cases which formed the basis for Wilson's original report of the disease there were 4 in which he was unable to obtain positive data. Consequently, I cannot see that the lack of a familial history in this case is a justifiable reason for discarding the diagnosis.

In response to Dr. O'Brien's objection to the diagnosis on the basis of Wilson's observation in his clinics that patients with disease of the striatum do not cross their legs: Again I merely refer to the original article by Wilson, for one has only to look at the pictures of the unfortunate victims to see that the legs of many are crossed, some in extension and others in flexion.

In answer to the question raised by Dr. Dolezal: Laboratory studies showed secondary anemia. In conclusion, it is noteworthy that in none of the cases reported by Wilson was the diagnosis of cirrhosis of the liver made during the life of the patient; it was only at necropsy that this was demonstrated.

A Case of Congenital Double Choreo-Athetosis Not Associated with Dementia. Dr. Louis J. Karnosh.

A woman aged 41, who was born at 7 months of gestation, shortly after an accident to the mother, did not attempt to walk until she was 6 or 7 years of age. She always has had a speech defect, but acquired a vocabulary at a slightly retarded age. She writes a fair hand, when not too excited by onlookers. When she was busy with home chores, she showed little or no athetosis. She not only took care of herself but did a great deal for her aged mother, who is nearly blind. There were no periods of unconsciousness or true convulsions. She went to school for two years, but obviously in such an emotional condition that she made little progress. She learned better at home when tutored by her mother.

The patient lies quietly in bed when not observed, but when there is any commotion about her, she enters into grotesque movements and tremors, with generalized ataxia. A grimace activates the facial muscles. All tendon reflexes were markedly exaggerated, which at once eliminates the typical chorea of early life, in which hypotonia prevails. There was a Babinski sign bilaterally. The Gordon-Oppenheim responses, however, were normal. There was no fixed hypertonus, the muscles rapidly changing from tonic spasm to extreme relaxation. The cranial nerves were normal: There was no nystagmus; the tongue was grossly tremulous but not atrophic. The eyegrounds were difficult to study.

The spinal fluid was under a pressure of 52 mm. of mercury and was cloudy; there was some blood (probably due to trauma from the needle); the Pandy reaction was 2 plus; the colloidal gold curve was flat, and the Wassermann reaction was negative. Encephalography gave good visualization of the cortical fluid pathways and of all major cisterns; the ventricles were not visualized. The skull appeared to be dolicocephalic.

The condition is regarded as a form of birth palsy. It may be unilateral as well as bilateral. It occurs as frequently without dementia as it does with retarded development, and in the severest forms of athetosis the patient may show a remarkably keen intellect. It is a fairly common expression of arrested embryonic development or early injury to the brain. Disturbances in motion constitute a characteristic feature of the cerebral palsies of children and are most often seen in early life, whether due to birth injury or to acquired factors.

The choreic movements after cerebral palsies are often confused with ordinary chorea. Paralysis and contractures, however slight, and exaggeration of the reflexes are generally sufficient to distinguish the condition. Genuine muscular atrophy is rarely present unless the spinal gray matter is involved. Little, Freud

and Sachs all maintained that rigidity, contracture, choreic or athetoid movements and paresis or paralysis constitute a graduated series of disturbances due to cerebral lesions in children.

When double athetosis exists, as it does here, the lesion is said to involve the basal ganglia rather than the cortex or the pyramidal tracts. All such disturbances are relative rather than absolute. Freud divided the cerebral birth palsies into: (1) universal spastic rigidity—a generalized defect; (2) paraplegic rigidity—a parietal defect; (3) bilateral hemiplegia—a defect of the white matter, and (4) bilateral chorea or athetosis—a ganglionic defect.

Porencephaly is the most common gross lesion. The acute picture is said to be due to thrombosis or hemorrhage in the deep parts, with cysts and sclerotic changes occurring later in life. At autopsy Sachs and Peterson observed atrophy, sclerosis and cysts in over one half of 78 cases of infantile hemiplegia, hemorrhage in one third, porencephaly in 2 cases and embolism and thrombosis in 12 cases.

The present attitude in respect to treatment is to look toward the miracles of neurosurgery for relief from these distressing hyperkinesias. Of timely interest is Tracy Putnam's operation—cutting the extrapyramidal tracts in the higher spinal segments—a formidable procedure, which is not to be used except in cases of extreme choreo-athetoid distortion.

DISCUSSION

DR. W. JAMES GARDNER: With regard to the neurosurgical approach in the problem of choreo-athetosis: I have not seen any remarkable therapeutic results. With the latest technic, namely, the Putnam operation, I have had no personal experience. However, a priori, it is my opinion that one merely exchanges one disability for another.

DR. JOSEPH L. FETTERMAN: This case is interesting in that the patient shows fairly normal intelligence in the presence of severe muscular symptoms. On first glance, practically all children with this condition appear queer and mentally retarded. However, when their intelligence is examined by appropriate series of psychometric tests a fair percentage are normal. Dr. Elizabeth Lord found that about 46 per cent of spastic children showed an average intelligence quotient. For 16 children tested in our clinic the intelligence quotients ranged from 30 to 130; 5 of the children had normal intelligence.

DETROIT SOCIETY OF NEUROLOGY AND PSYCHIATRY

H. A. REYE, M.D., *in the Chair*

Regular Meeting, Sept. 23, 1937

THE MAN THAT KILLS. DR. P. C. ROBERTSON, Ionia, Mich.

The Ionia (Mich.) State Hospital was created in 1883 as a civil hospital for patients with mental diseases, not as a penal institution. The population, now 906, is composed of four classes: prisoners who have become mentally ill (54 per cent); criminals on trial (26 per cent); patients with mental disease who have become homicidal (13 per cent), and psychotic ex-convicts (7 per cent). The present total population, 821 men and 85 women, gives the state as a whole a rate of 18 criminally insane persons per hundred thousand total population.

Homicide in the United States has increased 350 per cent since 1900; in 1935 the number of homicides was 9.2 per hundred thousand population. This rate is twenty-nine times that of the Netherlands, eighteen times that of England and three times that of Italy. In the United States there are eight times as many Negroes as white persons who commit homicide, this being the chief factor in the higher homicide rates in some southern states. There are four times as many

homicides by men as by women. Of all homicides in the United States 66.6 per cent are committed with firearms, as compared with 13 per cent in England.

This paper deals with the population of the Ionia State Hospital and does not include that of the penal institutions, although the difference in type of the inmates of the two classes of institutions is not great. Of the 906 patients, 186, or 21 per cent, have been homicidal. The clinical diagnoses in these cases are: neurosyphilis, 6.5 per cent; epidemic encephalitis, 5 per cent; alcoholic psychosis, 0.3 per cent; cerebral arteriosclerosis or senile psychosis, 3.5 per cent; psychosis with convulsive disorder, 2 per cent; psychosis with metabolic disease, 1 per cent; involutional melancholia, 15 per cent; psychoneurosis, 0.2 per cent; psychosis with organic disease of the brain, 1.5 per cent; manic-depressive psychosis, 2.5 per cent; schizophrenia, 32.5 per cent; psychopathic personality with psychosis, 16.5 per cent; paranoid conditions, 11 per cent; mental deficiency with psychosis, 8 per cent and unclassified psychosis, 2 per cent. Thus, persons with schizophrenia, psychopathic personality with psychosis, paranoid condition and mental deficiency, in that order of frequency, total 68 per cent of the homicidal inmates. The same four groups in the total patient population are represented in the proportions of 44.7, 9.3, 7.3 and 6.8 per cent, respectively, showing that although the largest homicidal group is that of the schizophrenic patients, the criminals most liable to commit homicide are the psychotic psychopathic, the paranoid and the mentally deficient persons.

Classification of the motive or emotional reaction behind the crime showed that the etiologic factors were most frequently uncontrolled anger, alcoholic brawls and deliberate intent to kill, each in 21 cases. Next in order were: sudden compulsive idea to kill, in 17 cases; continual quarreling, in 12 cases, and ideas of being poisoned, infidelity, revenge, robbery, burglary and self-defense, each in 8 cases. Several illustrative case histories are presented.

Review of the cases shows that (1) in case of many patients who commit homicide the circumstances leading up to the crime are frequently isolated moments when the time is ripe for such an act and that such a progression of circumstances might never appear again; (2) the most common causes are uncontrolled emotion of fear or hatred or lack of inhibition of an abnormal appetite for liquor or drugs, and (3) frequently a person who commits homicide has been a law-abiding citizen up to the time of the overt act. Thus, one must look primarily to abnormality in the emotional field and to disturbances in adjustment to living for the etiologic factors for homicide.

CIRCUMSCRIBED AMNESIA IN THE CRIMINALLY INSANE. DR. L. E. DUVAL, Ionia, Mich.

This paper describes a sharply defined amnesia for single events (crimes), usually described as hysterical, a reactionary situation syndrome or a hysterical fugue. The amnesia is characterized by rapid onset, variable duration and usually complete restoration of memory. It is seen in criminals who have committed murder, assault, rape, incest and other sex offenses. It usually occurs after a first offense and in persons of long-standing unstable personality, and as the climax of an emotional crisis. Memory is unimpaired except for the actual crime. Amnesia begins when the crime is completed, or shortly thereafter. It lasts from a few weeks to several years, with recovery which may be rapid or gradual. It does not resemble the amnesia of alcoholism, schizophrenia or organic diseases of the brain. It must be differentiated from malingering; this is ordinarily done by having the patient repeat his story at frequent intervals, while one looks for contradictions which the malingerer usually shows. At the onset of amnesia, complications of the Ganser syndrome, acute hallucinatory episodes, anxiety, fear states or confusion occur but rapidly subside, leaving amnesia as the sole symptom. There is usually lack of proper affect concerning the crime, even after memory returns. Hypnosis or psychoanalysis usually results in the development of paranoid reactions. Some patients, after memory is restored, attempt to cover up the fact by malingering. During the amnesic period the patient may have a blank memory

or may fabricate in an attempt to fill in the period for which he cannot account. Eight cases are described, and the paper concludes with a discussion of the medicolegal import of a type of amnesia which is usually attributed to malingering.

SOMATIC DISEASE COMPLICATING PSYCHOSES: REPORTS OF 2 CASES. DR. R. E. COOPER, Ionia, Mich.

Two cases are described in which a definite physical abnormality, other than disease of the central nervous system, influenced the mental condition. In case 1 the somatic disease complicated and obviously aggravated the psychosis, and in case 2 it precipitated the mental disease. In each case the mental picture cleared after the removal of the somatic abnormality.

CASE 1.—P. D., a man aged 32, was sentenced to life imprisonment on Sept. 15, 1923, after he had, with two accomplices, shot and killed a storekeeper during an act of robbery. He had previously been convicted of grand larceny and passing worthless checks, after which he was placed on probation for two years. Because of incompatibility with his stepmother, he had left home in youth, roamed the West, been periodically employed, fallen in with bad associates and participated in dissipation, rum running and, finally, murder. Two months after his admission to the prison, after having been disciplined for minor infractions of rules, he presented a situational reaction of prison origin, refusing to talk or eat, staring at the walls, picking pieces out of his mattress and pouring water on the floor and sitting on it. After his transfer to the Ionia State Hospital, on December 15, he exhibited stupor, restlessness and depression for one week. The staff diagnosis was: psychopathic personality with psychosis, and psychogenic stupor reaction.

On being returned to the prison, the patient for the first five years was contrary, restless, uncooperative, stubborn, irritable and bitter toward the warden and guards, and threatened to kill the first person who crossed him. In August 1930 he was operated on at the prison at Marquette for rupture of the appendix and remained in bed three months. Two months after the operation, he began to complain of chronic constipation, acute abdominal distress and cramps in the operative area. The abdominal pain became a continuous dull ache above the operative scar, and constipation increased. The patient remained despondent, morbid, suspicious and hypochondriacal, with delusions of persecution, and was a pathologic liar.

On readmission to the Ionia State Hospital, on Sept. 26, 1935, he was mentally clear and alert, but restless and worried about being returned to a hospital for mental disease. His cathartic habit of four years was now interrupted, and a program for control of constipation was instituted. He complained of ineffectual defecation, "clogging" of his intestines with poison, spasticity of the anal sphincter, passage of large amounts of mucus, repeated attacks of pain at the operative site and vomiting. For three weeks similar attacks recurred six or eight hours after meals, with increasing frequency. He was depressed and obviously worried about his condition. Psychometric examination revealed average intelligence, and his responses to abstract mental tests were good.

Physical examination showed moderate underweight, almost total blindness on the right due to retrobulbar neuritis, definite tenderness on pressure over the scar of the operative wound and considerable gaseous distention. Proctoscopic examination showed a severe grade of mucous colitis, with spasticity of the anal sphincter. Roentgenography, following a barium enema, showed rather marked gastroptosis, partial intestinal obstruction at the ileocecal orifice, delayed emptying time throughout the colon and multiple diverticulosis of the lower part of the sigmoid flexure. The diagnosis was: psychosis with somatic disease; partial intestinal obstruction from postoperative adhesions, and psychoneurotic symptoms with mild paranoid reactions.

Abdominal section on December 20, with the patient under general anesthesia, revealed that the cecum and ileum were bound down by firm bands of adhesions, some of which were 1 inch (2.54 cm.) in diameter and produced partial stricture at the ileocecal orifice; the lower portion of the ileum above the orifice was dilated, and the walls were thin. The adhesions were cut, the intestinal coils loosened and

bleeding points arrested, and the omentum was wrapped about the severed tissues. After a stormy convalescence, the patient almost immediately showed a more cheerful and optimistic outlook. One month after operation the former pain, vomiting and dyspeptic symptoms had nearly disappeared. His mental outlook was completely reversed. He was confident and cooperative and was desirous of returning to prison and making a good record. After convalescence he did good work in the occupational department, became regular in his habits and had a daily bowel movement without cathartics. Gastro-intestinal fluoroscopy on Feb. 20, 1936, gave essentially normal findings. He was discharged as recovered to the prison at Jackson, and at the last report was in good physical and mental condition—a steady worker in the prison dining-room.

CASE 2.—V. N., a man aged 34, who was admitted on information of assault with intent to kill, had been a steady, dependable worker on farms and in a canning factory. He married at the age of 18 years; he was devoted to his wife and four children and had no bad habits. In January 1926, a lesion of the lower lip, of four years' duration, which had previously been treated with acid by a charlatan, with resultant deformity, was operated on at the University Hospital, Ann Arbor, for removal of a carcinoma. Excision of the lesion and resection of glands in the neck resulted in severe destruction of the lower lip and disfigurement. The patient refused plastic repair after the excision. He immediately began to worry about his physical appearance, grew a drooping mustache and refused to eat in company because of unavoidable spilling of food from the mouth. Engrossed in his deformity, he neglected work, lost two jobs, interrupted his regular church attendance, became unable to support his wife and family, served thirty days in jail for horse stealing and was detected in passing forged checks. Increasing domestic friction led to suit for divorce by his wife, and in one of the now frequent arguments the patient made an impulsive assault on her, beating her with an iron bar and leaving her for dead. He was confined in the county jail on Oct. 10, 1932; during the following three weeks there developed an acute psychogenic reaction, with amnesia for the crime.

On admission to the Ionia State Hospital on October 29, he was first seen while lying in the sheriff's automobile, moaning and groaning; he was carried to the examining room, where he slouched in a chair, buried his head in his arms and refused to answer questions. He talked a little on the following day and more on the third day and became oriented and disturbed when informed by the physician of the circumstances leading to his arrest. He showed complete amnesia for the crime and for the three weeks spent in the county jail. He complained of severe occipital headache, spoke freely about his sensitivity regarding his personal appearance, attempted to conceal his lower lip in talking and worried continually about his wife, writing frequently for forgiveness but receiving no reply. The amnesia for the circumstances of the crime continued, but he adjusted well to institutional requirements. Physical and laboratory examinations revealed a somewhat unsteady gait, fine tremor of the fingers and an extensive defect in the lower lip, extending from the midline to the right corner of the mouth, with exposure of the lower teeth and gums and continual drooling of saliva. The Kahn reaction of the blood and spinal fluid was negative. Urinalysis, hematologic examination and blood chemistry studies gave normal results. The diagnosis was psychoneurosis, of an anxiety type. The cause was postoperative disfigurement.

On June 20, 1933, plastic repair was commenced, the operation requiring fourteen stages covering a period of nine months. The patient was extremely anxious to have this done and cooperated fully. He regained his normal composure and confidence, and although his wife had secured a divorce, he was anxious to return to society and to make a living for his children. He felt sure that he would never have another mental upset, saying that it was the first time in eight years that he could look people in the face without shame. On May 7, 1935 he was returned to court. The criminal charge against him was dismissed. He immediately obtained steady employment, and at the last report was working as chief mechanic in an automobile repair shop, in friendly and happy circumstances.

NEW YORK NEUROLOGICAL SOCIETY

Moses Keschner, M.D., *President, in the Chair*

Regular Meeting, Oct. 5, 1937

President's Address: Forensic Neuropsychiatry. Dr. Moses Keschner.

Dilatation of the Cavum Septi Pellucidi and Juxtaventricular Cavities. Dr. Amour F. Liber (by invitation).

From a review of the literature concerning the cavum septi pellucidi it appears that, in spite of considerable work on the subject, there still is no agreement about the early ontogeny or the adult histology. The origin of the cavum has been described in three ways, each theory still having its upholders. Accordingly, the cavum is: (1) a portion of the interhemispheric fissure, isolated by fusion of the marginal zone (Reichert); (2) a secondary cleft in glial tissue resulting from total concrescence of the medial portion of the pallium (Marchand), or (3) a cavity resulting from breakdown in the tissue of the primitive lamina terminalis (Hochsteter). The adult caval lining, likewise, has been described as connective tissue, endothelium, ependyma and neuroglia. Wolf and Bamford observed no mesenchymal tissue but a discontinuous layer of glia cells, which they termed pericaval cells.

A dilated cavum septi pallucidi extending from the genu to the splenium of the corpus callosum constitutes a rare variant, which is of interest to the clinical neurologist, neurosurgeon and anatomist. Accumulation of fluid in an unperforated cavum may cause intracranial hypertension and a syndrome characteristic of tumor in the midline. Dandy showed that diagnosis can be made by ventriculography and that puncture of a septal leaf at operation is efficacious therapy. Reports of 16 cases, in most of which the condition was discovered post mortem, were found in the literature.

In 2 of the 3 original cases reported here there were continuous cavities. In 1 there were an obliterated aquaeductus septi and two distinct cavities, both of which were greatly dilated. In all 3 cases the leaves of the septum were perforated, and the cavum communicated freely with the lateral ventricles. In 2 cases thin trabeculae traversed the cavum. In 1 case, in addition to the dilated septal cavity, there were large subependymal cavities bilaterally, in or near the head of the caudate nucleus. These juxtaventricular cavities were suggestive of abnormally persistent cava corporis striati, which Essick observed constantly in human embryos. No report of a case of this anomaly was found in the available literature. The lining of the cavum septi pellucidi and of the juxtaventricular cavities did not give the staining reactions of collagen, but was gliofibrillar, with occasional flattened pericaval cells. These data are in keeping with Hochstetter's account of the development of the cavum septi by interstitial liquefaction of the lamina terminalis. The same process was observed by both Essick and Hochstetter in the formation of the cava corporis striati.

DISCUSSION

Dr. Leo Davidoff: I wish to congratulate Dr. Liber on his scholarly and timely discussion of the problem of the septum pellucidum. This structure has recently acquired popular interest, especially since the development of encephalography and ventriculography and the study by these methods of the finer structures of the brain. In the so-called butterfly pattern of the ventricles in the anteroposterior encephalogram, the dense structure that divides the two lateral ventricles represents the septum pellucidum. This has been serviceable as a point of departure for the recognition of a number of pathologic conditions. One of the most common

of these is deviation of the septum. This occurs frequently, especially in cases of secondary hydrocephalus in which the injected gas is unevenly distributed in the two ventricles, and may have no significance. Every once in a while, however, ventricular injection of gas results in the filling of a single ventricle, and if the septum is pushed over in the direction of the midline, obstruction of the interventricular foramina is suggested. This is especially true if a day or two later, when the gas has become absorbed, a picture of the other ventricle reveals the opposite condition. This is of considerable importance in the diagnosis of tumor in the region of the third ventricle. Dr. Liber, however, has brought out a point in his paper which limits the value of this sign, that is, the frequent perforation of the septum. This is especially true when obstructive hydrocephalus has occurred. Under these circumstances, a fluid pathway exists between the two ventricles, in spite of the fact that the interventricular foramina may be completely obstructed.

The cavity of the septum pellucidum, when it exists, has arbitrarily been described as of two types: 1. The cavum septi pellucidi. An encephalogram shows three cavities, the two lateral ventricles and the cavum between them; the cavum is always filled with the gas, because, as Dr. Liber has shown, a perforation exists from either one side or the other or both, connecting it with the lateral ventricles. This is not infrequently seen in encephalograms. As far as is known, these perforations are purely anatomic curiosities and are usually not associated with symptoms, encephalography being carried out for some other reason. 2. The second variety, called a "cyst" of the septum pellucidum, is perhaps similar to the first, but the communication between the cavity of the septum and the lateral ventricles is lacking. In the encephalogram the two ventricles are separated by a considerable distance, and the space between is occupied by a dense shadow representing the closed-off cavum. This is seen relatively infrequently; when it occurs it is usually associated with symptoms of obstructive hydrocephalus and signs suggestive of a tumor in the region of the third ventricle. It is this variety that Dandy and Van Wagenen have described. It can be treated surgically by approach through the corpus callosum and incision in the lateral wall to produce an artificial communication with one of the lateral ventricles, in the manner in which it occurs naturally in most cases.

My colleagues and I have made another observation: When perforation of the septum results from hydrocephalus, especially in cases in which the interventricular foramina are obstructed, one finds gradual disappearance of the septum, so that the lateral ventricles appear with one large shadow representing both ventricles and nothing between them. We have come to recognize that such a picture is due to absence of the septum as the result of gradual enlargement of the perforation, and have proved at operation the lack of the septum in these cases. When the operator approaches the region of the interventricular foramina through one lateral ventricle, he is able to look directly into the opposite ventricle, with no obstruction. This led to discovery of the case of a young woman who had mental symptoms after encephalitis. Encephalograms were made for the purpose of determining whether any apparent pathologic change in the brain accompanied the condition; we found a shadow similar to those I have just demonstrated, with no line representing the septum pellucidum. The two lateral ventricles were represented by a single shadow. In view of the fact that there was no hydrocephalus in this case, we assumed that the single shadow represented congenital absence of the septum pellucidum. In the literature we found a report on the postmortem examination in a similar case. I doubt whether this condition has any clinical significance, but it is of anatomic interest and may be helpful in elucidation of the embryologic development of this structure.

Dr. Marcus Neustaedter: I shall limit myself to a discussion of the clinical phases in the 3 cases described by Dr. Liber.

Case 1.—No abnormal neurologic symptoms were shown. At autopsy there were diffuse cortical atrophy and a pseudocyst of the septum pellucidum.

Case 2.—F. H., a chronic alcoholic addict, was admitted to the hospital from the City Home in 1933 and was readmitted in 1936. He was mentally confused and

disoriented as to time, place and ordinary events of the day, and rambled incoherently. The pupils were unequal; the right was larger than the left and reacted poorly to light; tests for accommodation could not be made. There was central facial weakness on the left; the abdominal reflexes could not be elicited, and there were no pathologic reflexes or motor disturbances. Sensibility could not be determined. The patient improved slowly and was discharged. On Jan. 23, 1936, he was admitted in a state of deep coma, which had come on suddenly after he had complained of weakness four hours before. There were conjugate deviation of the eyes and retraction of the head to the right, a Babinski sign bilaterally and signs confirmatory of the diagnosis of cerebral hemorrhage; the fundi showed contraction of the vessels and pallor of the disks.

Autopsy revealed: multiple hemorrhagic infarctions and ischemic softenings in the right cerebral hemisphere; an old hemorrhage with scarring and atrophy of the left cerebellar hemisphere; cystic (communicating) cavity of the septum pellucidum, and absence of the gray commissure.

Case 3.—D. H. was admitted to the hospital on two occasions, the first being in 1929. There was a history of weakness and stiffness in both lower extremities of about seven years' standing. The right pupil was larger than the left and reacted sluggishly to light and in accommodation. The left palpebral fissure was narrower than the right. There were slight central facial weakness and left hemiparesis, with the superficial and deep reflexes more active on the left; no pathologic reflexes were elicited. Sensibility was intact. The fundi showed arteriosclerosis. Since there was no history of unconsciousness at this time, the diagnosis was hemiplegia of long standing due to thrombosis of the lenticulostriate arteries in the right internal capsule. The patient was discharged in 1934. He was readmitted on April 11, 1936, with a diagnosis of bronchopneumonia, and died on the next day.

Autopsy showed slight diffuse atrophy of the brain, moderate dilatation of the lateral ventricles, absence of the gray commissure and enlargement of the septum pellucidum, extending to the splenium of the corpus callosum; there was no evidence of hemorrhage or thrombosis.

It is, of course, impossible to diagnose this condition intra vitam.

Dr. Irving H. Pardee: Dr. Davidoff is familiar with a case in which we were both interested at the New York Neurological Institute—of a boy aged 10 years whose presenting symptom was precocious puberty. At this age his genital development was that of an adult. The habitus was otherwise strikingly hypopituitary in type. When he was 10 years old, he consulted me about the glandular disturbance; three years passed before permission for encephalography for confirmation of suspected intracranial tumor was obtained. A cyst of the septum pellucidum was found, and operation was performed, with successful results; convalescence was uneventful. However, there has been practically no increase in the boy's growth because the epiphyses are united, a not uncommon finding in the cases of early genital maturity. The symptomatology which Dr. Davidoff has described in relation to lesions of the third ventricle is exemplified in this case, with adiposity, growth disorder and macrogenitosomia praecox.

Dr. E. D. Friedman: This paper is interesting chiefly from the standpoint of anomalies in development. In the neurologic service at the Bellevue Hospital, my associates and I encounter frequently cases of cavity in the septum pellucidum. In the neuropathologic laboratory of Dr. L. D. Stevenson, it is not unusual to discover in sections of the brain a well developed cavity in this region. In these cases the observations are made casually and appear to have no clinical significance.

We had recently in our service a young man who had been suffering from epilepsy for many years; encephalography was performed, in line with our attempt to carry out such studies in as many cases of epilepsy as possible. We found the globular shadow between the anterior horns as described by Dr. Davidoff. Operation was suggested, but the family refused consent. The patient had no evidence of increased intracranial pressure or signs of a focal lesion. We finally decided that the encephalogram merely confirmed observations we had been making

post mortem and that unless the cyst is large and gives rise to increased intracranial pressure, there is no indication for surgical intervention.

DR. AMOUR F. LIBER: An important point which remains to be determined is the frequency curve for the size of the cavities in the septum pellucidum, and more accurate statistical data are needed concerning the size of the different types. I am at present making a study of this sort and am slowly accumulating cases. When I have enough cases for a statistical study, I hope to determine the frequency curve. It is particularly important to find out the size of the cavities at different ages, what the tempo of development is and when closure of the cavum septi pellucidi takes place. The cases I described were all those of older persons, and it is impossible to affirm that the anomalies were congenital. The finding of a simultaneous anomaly is strongly suggestive, but there is room for a great deal of further study.

CONTRACTIONS IN DENERVATED MUSCLES OF MONKEYS INDUCED BY FRIGHT AND REPRODUCED BY ACETYLCHOLINE. DR. MORRIS B. BENDER (by invitation).

Numerous studies have shown that autonomic nerve fibers exert their action through the medium of specific chemical agents. That epinephrine is liberated during emotional stress has long been known, but the liberation of acetylcholine during fright has not been demonstrated, although there are signs of parasympathetic activity. Since denervated muscle contracts when in contact with acetylcholine, it can be used as an indicator in the detection of acetylcholine.

The peripheral motor nerve supply to facial or ocular muscles in monkeys was completely destroyed. After a period allowed for the nerve endings to degenerate, contractions of the paralytic muscles occurred whenever the monkeys were angered or frightened. All observations were made on animals which were allowed to run loose in their cages. For simplification, contractions in the denervated muscles following fright will be designated by the term "fright reaction."

The fright reaction was obtained in every animal tested so long as the muscles remained denervated. The fright reaction was invariably augmented with physostigmine and could be reproduced by intramuscular injections of physostigmine and acetylcholine. Intravenous injections of acetylcholine produced contractions in the denervated muscles even without physostigminization. Atropine did not lessen the contractions induced by fright or those reproduced by acetylcholine. Epinephrine not only failed to yield contractions but inhibited those obtained with fright or a drug.

All available data suggested that contractions in denervated muscles induced by fright are due to a substance secreted in the body which is similar in action to acetylcholine. To determine the origin of this substance the local vasodilator nerve supply was stimulated and interrupted. Neither stimulation nor resection of the cervical portion of the sympathetic chain or of the infra-orbital nerve had any visible effect on the state of the denervated muscles. Extirpation of the superior cervical ganglion, even bilaterally, was also without effect, as was resection of both facial nerves and the ipsilateral oculomotor and trochlear nerves.

If the fright reaction is not due to secretion of acetylcholine from local nerves, one might postulate that it reaches the denervated muscles through the circulation. That Freeman, Phillips and Cannon could not demonstrate acetylcholine in the blood after stimulation of the vagus nerve does not detract from the possibility that during fright, when the entire organism is strongly activated, an excess of an acetylcholine-like substance is secreted in all parts of the body. A part of this excess may have escaped into the general circulation and thus have reached the sensitized denervated muscle. Other experiments have shown that the higher the animal in the phylogenetic scale the less conspicuous are the contractions in denervated muscles induced by fright and those reproduced by acetylcholine.

Irrespective of whether acetylcholine is formed locally or reaches the denervated muscles through the general circulation, contraction of the sensitized denervated muscle during fright indicates that acetylcholine is secreted during this state. The contraction of paralyzed muscle during fright is a phenomenon which illus-

trates one of the many mechanisms of body defense. It is suggested that during fright there is a general discharge of the autonomic nervous system and secretion of sympathetic and parasympathetic hormones. The interaction of the two phenomena influences the body in such a manner as to protect it in time of emergency.

DISCUSSION

DR. JOSEPH HINSEY (by invitation): These interesting and painstaking observations are stimulating in light of the concept of chemical mediation of nerve impulses. Dr. Bender's observations show that in primates discharges from the nervous system may produce the pseudomotor contracture in the unanesthetized animal. However, the origin of the contracture-producing substance is undetermined. Dr. Bender has indicated that it may be produced in general throughout the body, pass into the circulation and reach the denervated muscles. Concentration of acetylcholine in the general circulation sufficient to produce the contracture should produce other side effects, i. e., slowing of the heart, fall in blood pressure and salivation. None of these was reported in the experiments.

For acetylcholine to be built up in these amounts, the rapidity of action of the choline esterase postulated by the Dale hypothesis would have to be minimized beyond that shown in any previous experiments on unphysostigminized animals. The epinephrine in the blood stream, which Cannon and his co-workers have shown to be present in fright, should markedly antagonize any action of acetylcholine on denervated skeletal muscle. A number of other experiments, in addition to those described here, have shown a similar antagonism in pseudomotor contractures.

While Dr. Bender's evidence indicates that acetylcholine is the causative agent in these contractures, such building up of acetylcholine in the blood stream would not be compatible with the individuation and localization of cholinergic responses, as contrasted with the generalized action of adrenergic responses. To overthrow this generally accepted view, the evidence should be convincing and should involve direct analysis of the blood of a physostigminized animal during fright.

It seems that attention should be centered on consideration of whether the denervation is complete. Sympathectomy cannot be considered complete until the stellate ganglia and the cervical portion of the chain are removed. Furthermore, the possibility of pathways in the fifth nerve was not ruled out. While stimulation of the cervical portion of the sympathetic trunk gave negative results, this would not entirely eliminate this possibility.

In the craniosacral visceral efferent outflow there are cholinergic, and possibly adrenergic, fibers. In the thoracolumbar components there are both adrenergic and cholinergic fibers. The cholinergic fibers send a vasodilator supply to skeletal muscle. My colleagues and I have shown that the sympathetic cholinergic fibers are responsible for the Sherrington phenomenon. Recently, in our laboratory, Grant and Kirby have shown that the pseudomotor Heidenhain phenomenon in the tongue may be produced by stimulation of the cervical portion of the sympathetic trunk.

In 1885 Rogowicz described contracture in denervated facial muscle on stimulation of the cervical portion of the sympathetic trunk. Von Euler and Gaddum (*J. Physiol.* **73**:54-66, 1932) studied this reaction in detail in the cat. These phenomena, which have been studied in carnivores, are due to cholinergic fibers supplying the blood vessels of skeletal muscle. It may be argued that these responses are not present in primates. Bülbring and Burn (1937) reported that there are no vasodilator fibers in the lumbar part of the sympathetic chain of the monkey, but they did not report on the cervical portion. However, the evidence presented here would be much more convincing if complete cervical sympathectomy, including the stellate ganglia, had been done.

Dr. Bender has admitted the possibility of a local, as well as a generalized, production of acetylcholine. His work should stimuate further study of these phenomena in other forms.

DR. MCKEEN CATTELL (by invitation): Dr. Bender's studies are of great importance from a physiologic standpoint. I do not know that I can add anything to

what Dr. Hinsey has said, but I wish to go on record as agreeing with his views, particularly with regard to the hypothesis that it is unlikely that general activity of cholinergic nerves could be responsible for these results. It does violence to my idea of that mechanism in the body, and from a teleologic standpoint it appears improbable. The parasympathetic nervous system, unlike the sympathetic portion, is organized for local and specific action, and there is no obvious advantage in a generalized reaction involving these structures.

There is a highly developed mechanism for the quick destruction of acetylcholine. I talked yesterday with Dr. Nachmansohn, who has made some interesting studies in regard to the relative concentration of choline esterase in different organs (Marnay, A., and Nachmansohn, D.: Cholinestérase dans le muscle strié, *Compt. rend. Soc. de biol.* **124**:942, 1937); his observations indicate that the concentration is enormous in the nerve endings. According to his calculations, it is sufficient to account for almost instantaneous destruction of acetylcholine in skeletal muscle. In the blood stream there is also a considerable amount of esterase, so that the destruction there is rapid. I might also point out that the sensivity of denervated muscle in the cat and rabbit—I do not know anything about the monkey—is considerably less than that of autonomically innervated structures; there should, therefore, be other evidence of the effects of acetylcholine if, as Dr. Bender suggests, the fright reaction is due to generalized liberation of acetylcholine.

Dr. M. A. Kennard, New Haven, Conn. (by invitation): I have nothing to add to what has already been said. I have had the opportunity of observing Dr. Bender's animals during the past year and can say that the results obtained in what he terms the fright reaction are striking.

I think that the criticism made by Dr. Hinsey and Dr. Cattell is valid in that sufficient data have not yet been obtained to make it certain that the reaction is due to generalized liberation of acetylcholine rather than to liberation localized to the affected area. There are, however, other parasympathetic responses throughout the body following fright.

Dr. S. Bernard Wortis: I am reminded of a related significant clinical observation. I observed a young man who had peripheral facial palsy; electrical testing three and a half weeks after the original facial paralysis showed complete reaction of degeneration. In a subsequent panic reaction of schizophrenic type I saw his "paralyzed" face move. The panic reaction persisted for four weeks; at the end of that time he could not move his face at all. I am indebted to Dr. Bender for reporting his experimental evidence, which offers the first explanation I have known for the phenomenon of movement of a paralyzed face in case of fear associated with production of acetylcholine. The paper of Dr. Bender's is an important contribution to clinical humoral physiology.

Dr. E. D. Friedman: I wish to ask whether the secondary contracture which follows in the wake of Bell's palsy in some cases can be explained by the mechanism which Dr. Bender has just described. One is accustomed to think of residual contractures of this sort as due to nonmedullated innervation from the sympathetic system. I wonder whether Dr. Bender can offer an explanation for this contracture on the basis of his work.

Dr. L. H. Cornwall: In Dr. Bender's picture of the second or third monkey, when the fright effect was elicited and the palpebral fissure narrowed, there appeared to be enophthalmos. I wish to ask whether this was an illusion or whether the effect was noted in any of the animals.

Dr. Amour F. Liber (by invitation): I wish to ask Dr. Bender if he knows of any studies which might indicate a relation between acetylcholine and the chronaxia of degenerated muscle. It is known, after the work of Lapicque (L'excitabilité en fonction du temps, Paris, Presses Universitaires de France, 1926, p. 243) in particular, that many effects, such as curarization, which have previously been attributed to nerve endings are really due to changes in chronaxia.

Dr. Morris B. Bender: In answer to Dr. Friedman: I think that the contractions in formerly paralyzed muscles cannot be accounted for by the mechanism I

have described but that they may be due to faulty regeneration of nerve fibers. In answer to Dr. Cornwall: One could not observe whether there was enophthalmos, for the animal was too wild. Also, the narrowing of the palpebral fissure, which was due to the sphincter effect of the orbicularis palpebrarum muscles with a horizontal and vertical action, prevented visualization of the eyeball in question.

I cannot answer Dr. Liber. I did not measure chronaxia.

MENTAL DETERIORATION: ITS MEASUREMENT AND SIGNIFICANCE. DAVID WECHSLER, PH.D. (by invitation).

Mental deterioration may be said to be of two sorts—that which occurs after maturity, with the natural increase in age, and that which occurs at any age and is the consequence of organic disease or injury of the brain. Psychiatrists and neurologists have been concerned primarily with the latter and have almost entirely disregarded "normal" mental deterioration, except in cases of so-called senility. Psychologically, however, there is little difference between the two, except as regards the rate at which the deterioration occurs and, in the case of special traumatic injury, the number of mental functions involved. The loss of mental function met in "normal" old persons is similar to that in most organic disease of the brain, whether associated with vascular accidents of the brain (cerebral arteriosclerosis, apoplexy) or with impairment of brain tissue due to various toxic processes (alcoholism).

Mental decline is not characteristic of old age alone, as is generally supposed, but begins with respect to most measurable functions soon after the initial peak of mental accomplishment, that is, after the age of 25 or 30. Between 30 and 45 years of age the falling off is relatively small, but after that it is sufficiently important to be taken into account clinically in the case of most functions involving immediate retention, concentrated effort and practically all abilities in which the time element and speed of perception are important factors. In terms of test scores, the loss in old age is most marked in memory tests (retention of ideas, reproduction of visual patterns or repetition of digits, especially backward), in learning tests (substitution of paired associates test) and in practically all performance tests (form boards or picture completions). The loss is least marked in tests depending on acquired knowledge, such as the vocabulary and information tests (but not the tests for recent events).

In the estimation of the degree of mental deterioration there are two main difficulties. The first is that of obtaining a reliable measure of the actual endowment of the subject when examined. Up to the present the standard intelligence tests have been inadequate for this purpose, because they have been standardized primarily on children. This defect has now been remedied by a new form for adults (the Bellevue intelligence examination), which makes available norms for all ages up to 70. The second problem has been to find some method of estimating the person's original endowment. The general clinical method has been to guess at it from the social and economic history of the patient. Thus, if a patient was a college graduate, more was expected of him than if he was an illiterate day-laborer. While this method is serviceable in cases of marked deterioration, it is inadequate when one is dealing with the "average" person. What is obviously necessary is a quantitative basis for comparison, which would at once make allowance for normal deterioration and, at the same time, permit reliable measurement of significant excesses. For this one would need life curves for all abilities. Some data are now available for a number of these. Systematic studies of separate abilities now make it possible to estimate the discrepancies between the patient's probable native endowment and his present functioning, by comparing his performance in various types of tests. This is done on the theory that the decline in mental functioning does not occur equally in all fields. Thus, learning, retention and orientation are among the first to be impaired in mental deterioration, whereas language, information and general comprehension are among the last. Results like these have suggested the assembling of various types of tests consisting, on the one hand, of such mental abilities as remain relatively unimpaired and, on the other, of those which are

most conspicuously affected. Then, by comparing the levels of the two, one is in a position to obtain a qualitative measure of relative deterioration. Complete age curves for different abilities, together with examples of deterioration as revealed by various tests, are presented.

DISCUSSION

DR. KARL M. BOWMAN (by invitation): All realize that in the past intelligence tests have been associated particularly with children. The original tests were made on children. The mental ages ranged up to 12, 14 or 16 years, and it was thought that about 16 years of age was as high as one could go. The standardization by Terman for the age of 16 years represents the normal mental age for adults and an intelligence quotient of 100. The assumption was that one would not develop intellectually after that period. No one investigated to find the normal responses to intelligence tests at the ages of 20, 30, 40, 50 and so forth. One applied to adults these intelligence tests, which were standardized for children, and drew many conclusions from them. Some of the conclusions are certainly erroneous. The great value of Dr. Wechsler's contribution is that he has worked out a new type of intelligence test, the Bellevue intelligence test, which is for adults and is standardized for use after the age of 16 or 18 years. He has shown that a normal decrease in certain functions which are tested by standard intelligence tests starts at about the age of from 22 to 30, and that if one wishes to discover the intellectual capacities of a patient, one must modify the test according to his age. This is done in the new intelligence test. Therefore, I believe that the Bellevue intelligence test has certain values not found in any other. With other tests which have been worked out for adults, such as the Army alpha test and various performance tests, there is no such type of standardization. Dr. Wechsler shows the normal decline for persons as they grow older and so permits one to determine whether a person shows a greater amount of falling off than is allowable for his age. A difficulty with this test is that if one does not know what the man did at the age of 20, one cannot know what to expect of him at 40, 60 or 70, and I know no way of determining this. However, Dr. Wechsler at least takes into consideration these important factors. It is known that a man is at his optimum physical condition at the age of about 28. After this, baseball players, prize-fighters and professional athletes begin to go down-hill. Dr. Wechsler pointed out that the weight of the brain starts to decrease at the age of 28 and that the response to the standard intelligence tests begins to drop at about the same time, thus showing that there is an interesting correlation. Certain mental characteristics fail more rapidly than others, and this is the key to the study of deterioration. Vocabulary function tends to remain high as one grows old, while in certain types of performance tests mental function tends to drop off more rapidly. This gives a clue for working out the presence and something of the degree of deterioration. I believe this is an important contribution to the problem of intelligence testing and the study of deterioration.

DR. BERNARD SACHS: This discussion of the measurement of mental function interests me as to whether there is any use at all in the tests and whether one gains much by what has been said. One thing which I have heard, and which has been generally accepted, I have known for many years; that is, that from the moment a person is born he is approaching death. That is true; no one will deny it. I wish to know whether the tests included physicians as well as others; I presume they did. If so, it must have been satisfactory to the young medical men at the Bellevue Hospital to find that the highest intelligence rating is reached at about the age of 22 years and that from this time there is deterioration. Of course, there is nothing of the sort. Fortunately, Dr. Wechsler did not give the exact distinction between intellect and intelligence as demonstrated by these tests. If one makes the two synonymous, I object seriously to the conclusions drawn. Many others like myself, and I may claim a large experience, have never placed great value on intelligence tests, even in children, as a gage of the actual mental capacity or of the general mental condition. These arbitrary tests have been useful to a certain degree, particularly to psychologists, who have made the most of them, but to neurologists and psychiatrists they have often been of doubtful value. I do not

know what the Bellevue intelligence test stands for in case of the average person; I do not know whether there is any sense in trying to establish intelligence tests for adults. Less standardization, more thinking! Evidently, the material on which many intelligence tests were based was gathered from men drafted for military service, and the conclusions that were drawn must be applied carefully to the rest of the population. I do not wish to be too critical of this work. It is interesting to us of the medical profession to have some one from the outside look in on us, see what we are doing and try to interpret things for us, and we should always be willing to be criticized by outsiders; the psychologist, however, is thinking of one thing, and medical men have many other things to take into consideration. Take the case of senile deterioration. All know when a person is deteriorating and that he deteriorates particularly in certain respects. That which is marked in a senile process is slowness of reaction. Every one had a laugh, as I did—especially as a Harvard man—when the newspapers reported that President Lowell was refused his automobile license because of his slow reaction time. This slow reaction time is, of course, an important factor in general senile deterioration, but it may be marked without any other signs of mental senility. Senile deterioration is made up of a great many factors, and all will allow that there is great individual variation. Some men begin to deteriorate at the age of 20, and others live a little longer before they show any signs of deterioration. I am interested in the purely psychologic aspect of these tests. I question their value, their utility in psychiatric practice. By the way, I hate curves of this sort. Curves may be of interest, but they are apt to be misleading. I am appreciative of Dr. Wechsler's efforts and am pleased to have heard his paper.

DR. PAUL SCHILDER: I think that Dr. Wechsler's paper is exceedingly interesting and that it is helpful in finding at what age human faculties start to decline. Most men think that mental deterioration starts at an age which they have not reached and that they have at least five years before their faculties will decline. The older they get the later senile deterioration begins, in their opinion. I am opposed to general abstract connotations. When Dr. Wechsler says that in general mental capacities deteriorate after 30 years of age, I am skeptical, but there can be no question that he has shown that some functions become defective after this age. He has himself demonstrated that some functions do not diminish; perhaps new tests will show that some become better; so one should not generalize. One should study individual problems. One is here not to judge whether old persons are of any use but to determine their function in society. That is a problem which has never been solved. Tests are valuable because they give hints. And they furnish facts. Dr. Sachs does not believe that Dr. Wechsler has presented facts. I disagree with Dr. Sachs concerning "facts." I should like to emphasize that, after all, an observation is a fact, and Dr. Wechsler has observed and tested many hundreds of persons.

DR. BERNARD SACHS: I do not question the facts; I question the conclusions.

DR. PAUL SCHILDER: The conclusions of Dr. Wechsler are based on a great number of facts, and I do not see how one can question them. He has proved that some functions become defective when a man becomes older. So much as to the theoretical aspect of the problem. Dr. Sachs, with whom I must disagree again, is of the opinion that mental tests are of no use to the practical medical man and the psychiatrist. I think that that is again a generalization. I cannot doubt when Dr. Sachs says that they are of no use to him, but there are many in psychiatric practice who could not get along without psychometric tests. No estimation of a child's intelligence should be made without intelligence tests. They have proved their value from the practical side, and they are almost invaluable for appraising the social aspect of intelligence. I do not think one should rely on impressions. When one goes into a large children's ward, such as that at the Bellevue Hospital, one sees what one can do with these tests. I think one has no right to doubt the wisdom of the law which demands that intelligence tests be made before persons are sent to institutions for the defective. This is a social problem of the utmost importance, and one should keep that in mind.

I also cannot subscribe to the view that Dr. Wechsler's contribution has merely theoretical interest. One should not say that anything which has theoretical value is useless from a practical point of view. There is no sharp cleavage between practice and theory. The problems with which we as psychiatrists are confronted force us to determine whether or not a given person is deteriorated, and in such cases I do not like to rely on impressions. One must know what a person belonging to a certain age group can do, and it is important to know his capacity at specific ages. I think that curves are necessary, and I am grateful that Dr. Wechsler has shown such interesting curves. I wish to say that in general one should not judge senility as a defect. One should try to find a place in society for the senile person and for the old person in general. There is no question that old people are useful; perhaps Dr. Wechsler has given the impression that he does not like old people because of his great interest in the young. I think that one is justified in drawing conclusions from these curves, that it is important that one secure measurements in intelligence tests and that Dr. Wechsler's attempt is of great practical importance.

DR. A. L. BENTON (by invitation): I wonder if in the standardization of an intelligence test for adults one must not take into account social classes and occupational levels and if one must not have separate norms for various socio-economic levels in order to secure an adequate basis for the evaluation of a patient's test performance.

The discrepancy found between the score vocabulary and for language function and the scores in tests for other functions is interesting. It has been reported on by previous investigators (Jones and Conrad: *J. Genetic Psychol.* **13**:233-298, 1933. Babcock, Harriet: *Arch. Psychol.*, 1930, no. 117, p. 105; Dementia Praecox, New York, Science Press, 1933. Schwarz, R.: *Am. J. Psychiat.* **12**:555-560, 1932. Wittman, P.: *J. Abnorm. & Social Psychol.* **28**:70-83, 1933). I wish to point out that this discrepancy may be useful in evaluating the status of young persons of superior capacity, for example, a young college person. The test performance of such a person might compare not unfavorably with the established norms for the general population, in spite of impairment in mental function, and so this impairment would not be apparent. Here a discrepancy between performance in tests for language function and that in tests for other functions might be of significance.

I wish to ask Dr. Wechsler which "block design" test he used.

DR. ABRAM BLAU: I wish to raise the question of the correlation of the weight of the brain and intelligence. Many investigators have discovered no significant relation.

With regard to the growth curve for the weight of the brain: Dr. Wechsler's statistics show that the brain reaches its highest weight at the age of about 20. I have found in the literature (Donaldson, H. H.: The Growth of the Brain, London, Walter Scott, Ltd., 1899. Vierordt, H.: Anatomische, physiologische und physikalische Daten und Tabellen, Jena, Gustav Fischer, 1906. Wertham, F., and Wertham, F.: The Brain as an Organ, New York, The Macmillan Company, 1934) that most statistics indicate that the full weight of the brain is attained below the age of 10 years, in most cases at the age of 8. This point probably can never be settled. In every case in which postmortem material is used, the problem whether the brain has reached its acme must be considered. Estimations of the weight of the brain during life have thus far been unreliable.

DR. S. BERNARD WORTIS: I am sure that Dr. Wechsler will agree that in the individual case the weight of the brain and the intelligence cannot be correlated.

He spoke of choosing persons from various social strata of the population; I wish to know how many he used as normal controls. I believe it is useful to have a good standard intelligence test for adults, and I agree that no single test is of value when used alone. The intelligence test acts as a mental hurdle, just as a vital capacity test measures physical ability. Furthermore, one must remember that mental tests are by no means complete, nor do they, at this date, claim to measure all aspects of mentation. Their incompleteness, however, should not con-

demn them. They should be used with recognition of their limitations and, at the same time, with acceptance of what little they have to contribute to the understanding of a person and his abilities.

I wonder (and this is a delicate question) how Dr. Wechsler feels about neuropsychiatrists themselves giving the intelligence tests. The neuropsychiatrist, while working with a patient, can gain many impressions of value which might be missed by the nonpsychiatrically trained clinical psychologist. I prefer to give the intelligence tests myself.

I also wish to know on how many cases Dr. Wechsler based the standard chart showing the specific psychologic defects in the various psychoses. Does he believe that the amount of material is sufficient on which to base such a chart and such conclusions? My own feeling is that they will be much modified by the tests of time and additional experimental observations.

Dr. Amour F. Liber (by invitation): From the pathologic point of view there is a marked difference between the brain of a person with senility alone and the brains of persons who have shown evidence of mental deterioration. In cases of mental deterioration there are almost invariably shown piling up of lesions, generally attributed to vascular disturbance, or the changes seen in the senile psychoses. I had occasion to study in Paris the brain of a 101 year old woman. Her mentality was well preserved shortly before she died. She had been observed for two months. Her brain showed far less change of the type generally observed in old age—arteriosclerotic and lipoid changes and senile plaques—than is usually seen in brains of much younger persons. In this case there was lack of atherosclerosis, not only of the cerebral but of other arteries. I think deterioration is due not to age as such but to the piling up of lesions and that these lesions vary with the individual person. Naturally, they will be more frequent the longer a person has lived and the longer time he has had to contract disease.

Dr. David Wechsler: With regard to the relation between weight of the brain and intelligence: I thought I had made clear that the two curves were not presented in order to prove any correlation between these two variables. Obviously, one could speak of a correlation only if the measures recorded had been made on the same persons. This, of course, was not the case. The fact, however, that the slope of the variation of brain weight with age shows the same characteristics as that of the variation of intellectual ability with age indicates that one is dealing with a trend of the same sort. In the sense that the weight of the brain may be looked on as an expression of the capacity of the organism, its decline with age may be regarded as the same sort of process as that which occurs with the decline of any ability, such as the ability to throw a ball or to solve a mathematical problem. The interesting thing is to note that the beginning of a decline in all abilities occurs approximately at the same age level.

As to the age of maximal brain weight, which Dr. Blau has questioned, I should say that the high point in the curve which was generally seen corresponds with nearly all statistics with which I am acquainted. The data which were used in the slides were those of Rössle and Roulet, as cited by Wertham (The Brain as an Organ, New York, The Macmillan Company, 1934). Dr. Wertham, who spent considerable time in reviewing the literature on the weight of the brain, assures me that these were the best he was able to find, and I can add only that the maxima which they give are in accordance with those of Pearl (Studies in Human Biology, Baltimore, Williams & Wilkins Company, 1924).

As regards the number of cases used in the standardization of the Bellevue test, the statistics, up to the present, are based on more than 3,000 cases, in a little over 1,500 of which the patients were between the ages of 20 and 65. This group constitutes, so far as I know, the largest number of adults ever used in the standardization of an individual intelligence examination. For the standardization of the test, the method used for the selection of adult subjects was that for the determination of vocational distributions of American adults as classified in the United States Census for 1930. Concretely, this means that it was tried, as far

as possible, to get about the same percentage of skilled and unskilled laborers, clerical workers, professional workers, etc., as are represented in the general classifications of the United States Census.

The table about which Dr. Wortis inquired is a poor one; I included it as an illustration of what one obtains when one tries to make a differential diagnosis by means of test batteries. This table is a composite obtained from data made available from various reported studies. It is far from definitive and undoubtedly will require alteration with accumulation of further studies, but it is the best illustration of data of this kind now available. The mental disorders represented are those of patients who, as is known, are extremely difficult to test; all this being taken into consideration, however, the data show that in certain mental disorders there is impairment either of different groups of functions or of the same functions in more marked degree. Thus, to take what was already familiar before tests were used, the table shows that patients with alcoholic psychoses of the Korsakoff type gave evidence of marked impairment in tests for memory for recent events and in those involving general learning ability. The table also shows peculiar differences in the functioning abilities in other types of disorders, but whether a result of this kind can be used for differential diagnosis is doubtful. More data are necessary, and one of the great values of the age curves is that they may enable one to obtain more useful batteries.

With reference to the question whether psychiatrists and neurologists should give their own psychometric tests: I am in accord with Dr. Wortis as to the advantage of doing so, provided the physician is thoroughly familiar with the necessary technics. These technics, however, cannot be acquired, as some physicians seem to think, by reading a book on psychometrics and then observing three or four patients. As with every other kind of examination, the administration of a psychologic test is an art. The average graduate student in psychology spends anywhere from six months to a year and a half in learning how to give a psychometric test with reliability. I do not think that the average physician can do it in less time.

I should have replied to Dr. Sachs first, but his criticism was so wholesale and the questions he posed are so weighty that the lateness of the hour precludes any serious attempt to answer him at this time. I wish, however, to take a moment to supplement Dr. Sachs' account of President Lowell's inability to obtain a driver's license in Massachusetts. According to my informant, the reason that he was refused one was not alone because of his slow reaction time but because of his continued record of accidents.

Book Reviews

Der Kumpan in der Umwelt des Vogels (Der Artgenosse als auslösendes Moment sozialer Verhaltungsweisen) [The Companion in the Environment of the Bird: The Fellow-Member of the Species as a Motivating Factor in Social Behavior]. By Konrad Lorenz. J. f. Ornith. **83**:137-213, 1935. **The Companion in the Bird's World.** By Konrad Lorenz. Auk **54**:245-273, 1937.

Many psychologists and psychiatrists who deal with human beings become engulfed in the complexity of their material and never become acquainted with the simple and important facts of "natural history." Training in the simple biology of barnyard and forest is a great educational advantage. The fact that many leading psychologists are urban products, knowing little of these biologic fundamentals, has led to much misunderstanding of what an instinct really is and to much vague use of such terms as "instinctual."

Recognizing this weakness in modern psychology, it was with delight that the reviewer came on these two papers by Lorenz. He has made extensive observations on birds, both wild and domesticated, captive and free, and has come to conclusions which seem to upset orthodox beliefs of the comparative psychologists and to illuminate obscure parts of Darwin's explanation of the survival value of certain structures and behavior patterns.

Conspicuous among Lorenz' contributions is his elucidation of the meaning of the various structures and habits of birds that Darwin lumped under the term "secondary sex characters." He rids himself of the anthropocentric attitude that a bird does anything because it "learns" or "thinks" or "sees" that so and so is the case. He points out that instinctive actions are not directed toward a goal by the bird carrying out this action (even if, racially speaking, the goal is obvious). "If an instinctive action is directed toward a particular object, its successful performance is independent of the animal's perceiving this object as a 'thing,' that is, as a permanent unit of space and time as we would perceive it. All that is needed on the part of the animal is the disposition to respond with just that reaction to certain stimuli characteristic of its particular object. . . . The receptory part of the animal's reaction responds to a small but characteristic combination of stimuli, very much in the way in which a highly selective wireless receiving-station is attuned to a particular wave-length. This perceptory correlate to a very definite combination of stimuli has been termed by William McDougall the 'innate perceptory inlet.'

"It is an old but fitting metaphor to liken the releasing set of stimuli to the *key*, and the innate perceptory pattern to the *lock* of the instinctive reaction. Even more appropriate is the simile of a combination lock that cannot be opened except by a definite series of manipulations which, by reason of their general improbability, it is practically impossible to find by chance. The relation of the particular form of the lock to the key that fits it, or of any innate perceptory pattern to the set of stimuli to which it responds, is ever a compromise between greatest possible simplicity and greatest possible general improbability."

In other words, the combination of stimuli can be very simple indeed, but that especial combination must be improbable in the given animal's environment, except under the circumstances appropriate to the specific reaction. For example, a tick responds to butyric acid plus a temperature of 97 F. by biting; in his environment this almost invariably means mammalian skin, and it works. "The means evolved for the sending out of key-stimuli may lie in a bodily character, as a special color design or structure, or in an instinctive action, such as posturing, 'dance' movements and the like. In most cases they are to be found in both, that is, in some instinctive acts which display color schemes or structures that were evolved exclusively for

this end. All such devices for the issuing of releasing stimuli, I have termed *releasers (Auslöser),* regardless of whether the releasing factor be optical or acoustical, whether an act, a structure or a color.

"The essential general improbability of all releasers is brought about in a way characteristic and very similar even where they have been evolved independently in very different forms of animal life. Throughout the universe it is order that is improbable while disorder, chaos, entropy or whatever one chooses to call it, is what we should expect from the laws of probability. I do not think it too far-fetched an explanation to suppose that the striking orderliness and regularity which so strongly appeals to our sense of beauty in the coloring, the notes and the display movements of so many animals, especially of birds, has its source in their nature as releasers and in the general tendency of all releasers to develop in the direction of the more improbable. This would also explain the astonishing rhythm that we meet in very nearly every releasing action. The more or less pure spectral colors which so often appear in color patterns functioning as releasers, very probably also find their explanation in this way, since the reflection of one wave-length among the wave-mixture of white light is in itself rather improbable, so improbable indeed that color alone may, in some cases, function as a releaser."

Such a theory of beauty, based on release of primitive patterns in man's make-up, seems much more in line with modern psychologic knowledge than the geometric intricacies of the "dynamic symmetry" of some modern artists. "All these movements and structures which function as releasers, by their essential quality of rhythmic regularity, have appealed strongly from time immemorial to the sense of beauty in man. It is no wonder that a vast amount of theorizing has been spent on their behalf. Darwin, in his work on 'The Expression of the Emotions in Man and Animals,' has indeed come very close to our conception of releasers, yet it is strange that . . . he could not believe any bodily organ was ever evolved for their special use. He states expressly that not a single facial muscle was ever differentiated in monkeys for the sole end of expressing some emotion. Contrary to this, we must state that we have good reason to believe that not only muscles, but very complicated structures in some species, have been evolved for the purpose of expressing one single emotion, or to be more precise, of transmitting this emotion to a fellow-member of the species. A good example of this is the erectile crest in all night herons, evolved for the purpose of indicating peacefulness, and comparable in its function to the tail-wagging of a dog."

Lorenz brings out interestingly the point that the inherited coordination of movement in the releasing reactions, the ceremony that starts a certain form of behavior, is usually older phylogenetically than the structures and colors of the parts of the bird used in these ceremonies. For example, all grebes depress the feathers of the neck and erect the feathers of the head during certain ceremonies. Each species of grebe, however, has its special arrangement and colors of the erected feathers. Apparently, the structures developed after the function had long been in general use by the forefathers of the genus.

In social animals the "releasers" are of great importance in calling forth concerted action—escape, attack, etc. "All those functions of coordinating the behavior of the individual members of society which, in the human species, represent one of the chief tasks of speech, are performed either by releasing ceremonies or by the transmitting of specific excitation which we have just described.

"There is no sharp boundary line between the simple transmitting of excitation, as we may say, 'by contagion' and releasing actions in the strict sense of the word. Responding to a certain reaction of a fellow-member of the species by reacting in the very same way is evidently wholly innate."

Perhaps some human reactions, such as "mob psychology," could be better understood if one looked for specific releasers, rather than higher psychic processes, as the cause. The differences in inborn receptory patterns, conditioning and learning are nicely brought out in Lorenz' discussion of von Uexküll's theory of the companion relations of animals. For example, the parent-companion of a newly hatched gosling is the first object he sees above him during his moments of drying off, after emerging from the shell. If he is hatched in an incubator and sees a

man, his following reactions are set, and he will ardently follow a man and pay no attention to his own mother if he meets her later on. Other startling instances are given: "Heinroth failed to breed hand-reared Great Horned Owls, Ravens and other birds, for no other reason than that these tame individuals responded sexually to their keepers instead of to each other. In a very few cases known, the bird whose sexual reactions were thus directed toward man, finally accepted a fellow-member of the species which, however, was always regarded as a rather poor substitute for the beloved human and was instantly abandoned whenever the latter appeared. Portielje, of the Amsterdam Zoological Gardens, raised a male of the South American Bittern (Tigrisoma) who, when mature, courted human beings."

Lorenz once hatched a brood of muscovy ducks under a pair of graylag geese. The parent-child relations in this artificial family dissolved sooner than is normal for either of the two species, owing to hitches in mutual understanding which occurred because the key and lock of the releasers and the innate perceptory patterns of the two species did not fit. From the seventh week of their life, however, the young muscovies had nothing more to do with their former foster-parents or with any other graylag geese, but behaved socially toward one another as well as toward other members of their species as a normal muscovy duck should do. Ten months later the one male bird among these young muscovies began to display sexual reactions and, to Lorenz' great surprise, pursued graylag geese instead of muscovy ducks, striving to copulate with them, but he made no distinction between male and female geese.

These reactions are not like the ordinary "conditionings" of learned reactions; but Pavlov was working with a different reflex level and with mammals. Lorenz calls this sort of laying down of reaction patterns "imprinting" and describes the points in which this process differs from what is called associative learning. (1) The process is confined to a definite period of individual life, a period which in many cases is of extremely short duration. (2) The process, once accomplished is totally irreversible, so that from then on the reaction behaves exactly like an "unconditioned" or purely instinctive response. (3) The releaser mechanism is often completed long before the reaction itself has become established. (4) "In the process of imprinting, the individual from whom the stimuli which influence the conditioning of the reaction are issuing does not necessarily function as an object of this reaction. In many cases it is the object of the young bird's begging-reactions, or the following-reactions, in short the object of the reactions directed to the parent-companion, that irreversibly determines the conditions which, more than a year later, will release the copulating reactions in the mature bird." Lorenz thinks it unwise to widen the conception of learning to include imprinting. "Such an increase of its content would bring the conception of associative learning dangerously near to including inductive determination as well, and experience has shown that this kind of stretching the boundaries of a conception is apt to destroy its value. This is exactly what has already happened to the conception of the reflex and to that of instinctive action."

These papers are well worth a careful study by the psychiatrist. The first is long and somewhat wordy and is difficult reading, but it is full of interesting observations direct from nature. It gives food for thought, and perhaps for fruitful speculation about some human reactions—especially the love reactions. One wonders how early these aversions and tropisms may be laid down and how irreversible they may be. Roughly, a gosling at the time of hatching corresponds to a child 2 years old; so differences must be evaluated, as well as analogies; but be the species ever so different, the pattern of instinctive behavior seems to follow certain laws.

The second paper is a good review in English of the monographic paper and is adequate for most psychologists, unless they are interested in looking up the many interesting examples described in the monograph.